



# Metage2Metabo: metabolic complementarity applied to genomes of large-scale microbiotas for the identification of keystone species

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# Metage2Metabo

metabolic complementarity applied to genomes of  
large-scale microbiotas for the identification of  
keystone species

Arnaud Belcour\*, **Clémence Frioux\***, Méziane Aite, Anthony Bretaudeau, Falk Hildebrand, Anne Siegel

Source code: <https://github.com/AuReMe/metage2metabo>

Documentation: <https://metage2metabo.readthedocs.io/>

Preprint: <https://doi.org/10.1101/803056>



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# Context

## Metagenomics flooding:

- Newly-discovered (uncultured) microbes/taxa in microbiota
- Assemblies of numerous new reference genomes
- Incoming golden era of Metagenome-Assembled Genomes (MAGs) and metagenomic species

→ **Collections of thousands of genomes/MAGs**



[Almeida et al 2019](#),  
[Nayfach et al 2019](#),  
[Pasoli et al 2019](#),  
[Parks et al 2017](#),  
[Almeida et al 2019](#)

Rely on relevant modelling approaches to tackle:

- **incompleteness** of poorly-studied genomes
- **impossibility to manually curate** thousands of metabolic networks (GSMNs)
- The **high combinatorics** brought by the analysis of all possible communities in the initial collection

→ **Network expansion algorithm** to model producibility



[Handorf et al 2005](#),  
[Van der Ark et al 2017](#),  
[Bernstein et al 2019](#)

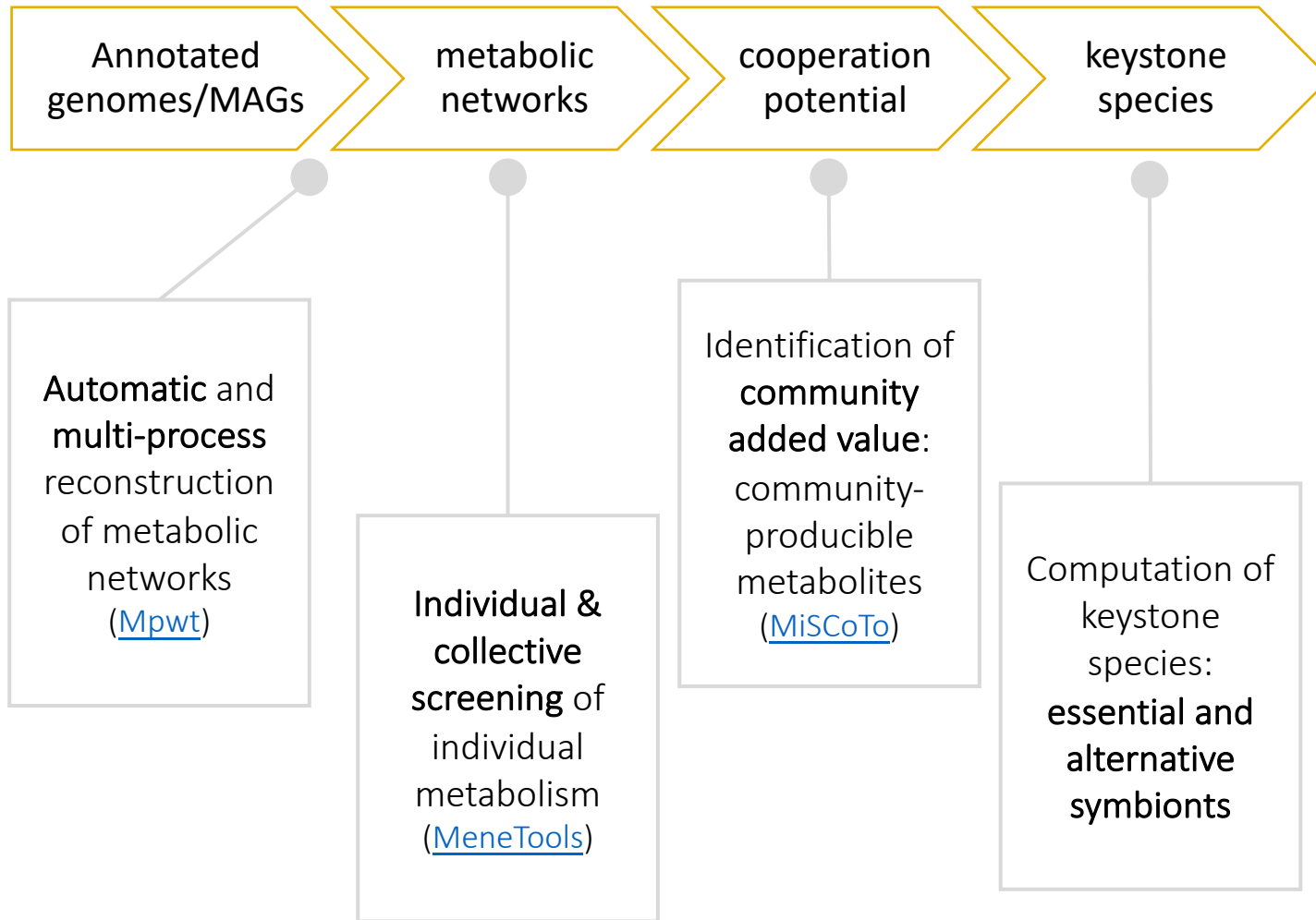
**Going beyond « who is there? »** in metagenomics datasets and large collections of genomes

- What can microbes do?
- What does putative cooperation between microbes brings to the community?
- Which microbes matter most for specific functions?



[Edgar et al 2017](#),  
[De Oliveira Martins et al 2020](#),  
[Sun et al 2020](#)

# Workflow



**M2M reconstructs metabolic networks for genomes/MAGs and screens the complementarity of metabolisms in a large community.**

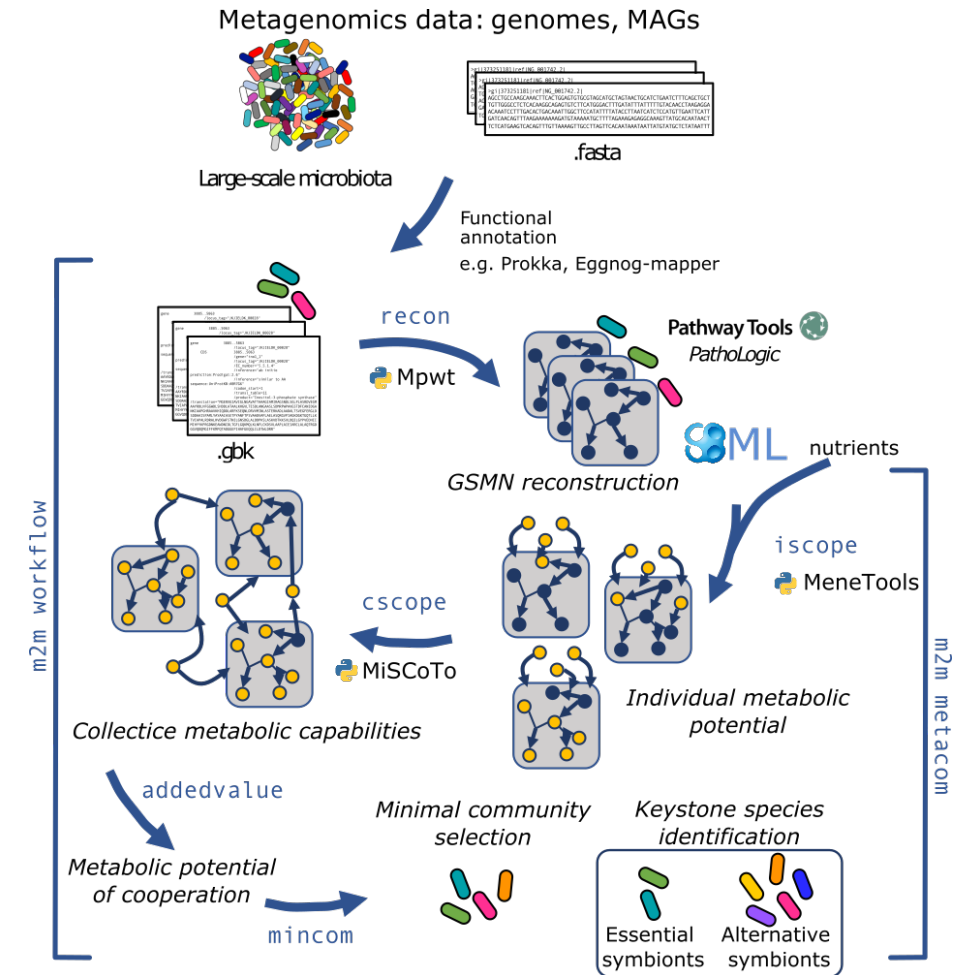


Fig. 1: flexibility of m2m's global workflow. The metacom command can run the workflow using existing metabolic networks (SBML)

# Application to datasets

Keystone species (KS) = *microbes occurring in at least one minimal community ensuring the producibility of a set of target metabolites from given nutrients*. Efficient solving: no need to enumerate all communities to retrieve them.

KS = essential symbionts (ES) + alternative symbionts (AS)  
*ES are found in every minimal community*  
*AS are found in some minimal communities*

913 cow rumen MAGs ([Stewart et al 2018](#))  
 1520 draft bacterial reference genomes ([Zou et al 2019](#))

↓  
 m2m workflow

Insights:

- Metabolic networks from reference genomes and MAGS display similar characteristics (Fig. 2)
- M2M metabolic screening and KS identification are robust to low genome degradations (Fig. 3)

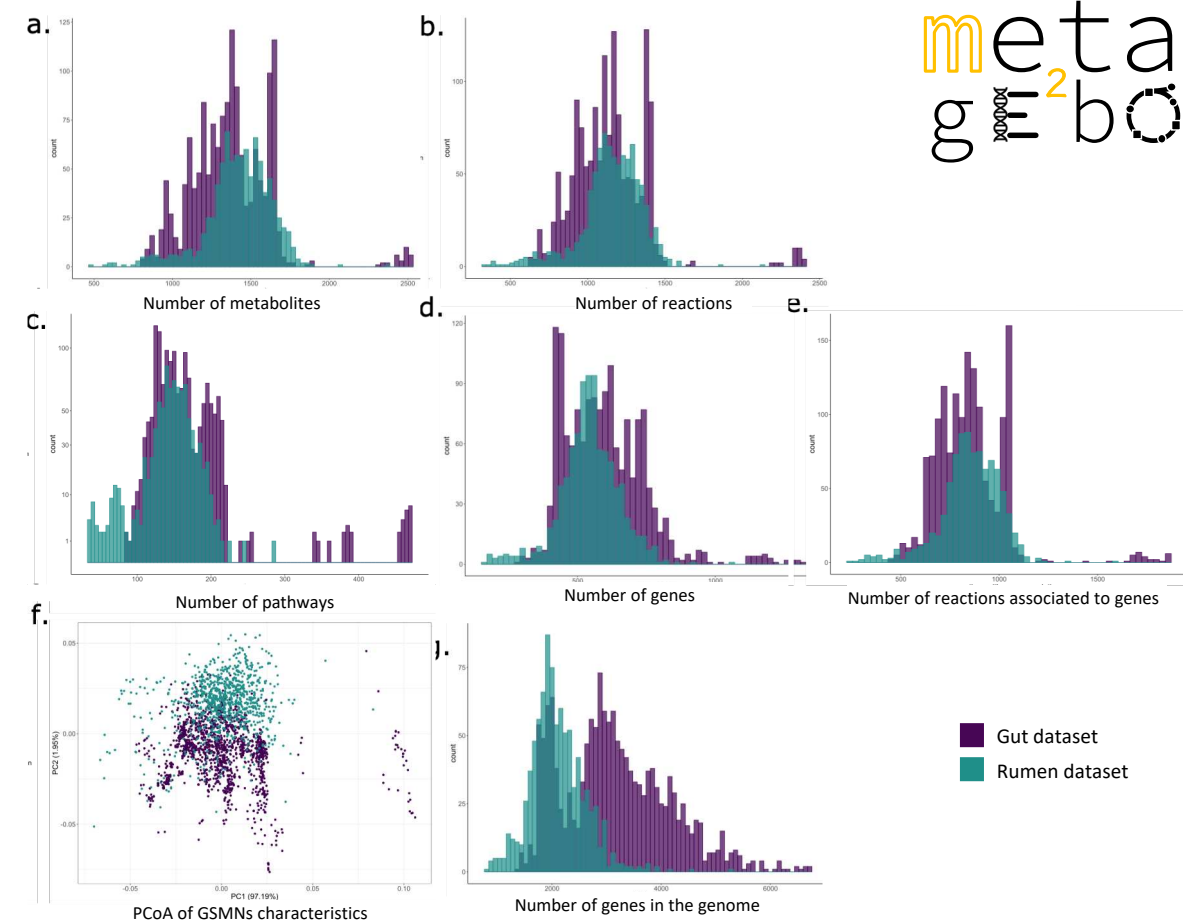


Fig. 2: Comparison of GSMNs from both datasets

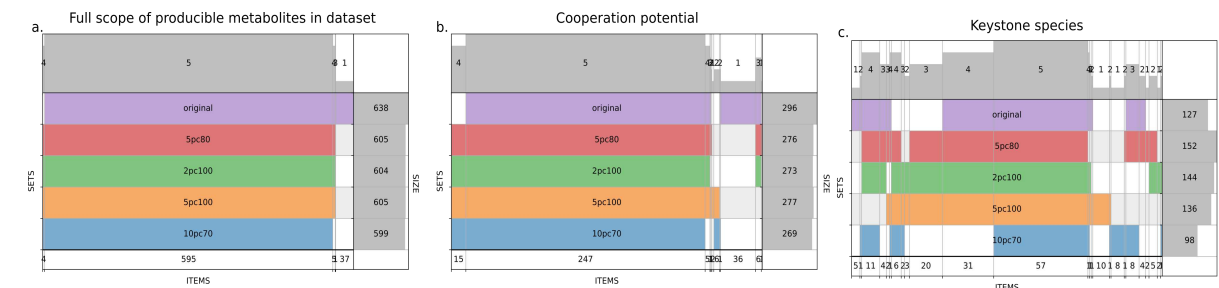


Fig. 3: Robustness analysis following MAGs degradation for the rumen dataset (upper row: original genomes, up to down: increasing genome degradation)

# Analysis of gut communities

Collection of genomes = 1520 draft bacterial reference genomes ([Zou et al 2019](#))

Nutrients = typical EU diet (qualitative)

Targets = metabolites producible only through cooperation processes, grouped by categories

→ Enumeration of all minimal communities with m2m-analysis to study putative associations of microbial metabolisms

		Firm.	Bact.	Acti.	Prot.	Fuso.	total
<b>all</b> (156 targets)	KS	41	47	103	12	2	205
25 bact. per community	ES	8	0	1	2	0	11
not enumerated	AS	33	47	102	10	2	194
<b>aminoacids and derivatives</b> (5 targets)	KS	142	52	0	27	6	227
4 bact. per community	ES	0	0	0	0	0	0
120,329 communities	AS	142	52	0	27	6	227
<b>aromatic compounds</b> (11 targets)	KS	52	0	0	20	0	72
5 bact. per community	ES	2	0	0	1	0	3
950 communities	AS	50	0	0	19	0	69
<b>carboxyacids</b> (14 targets)	KS	16	13	0	28	2	59
9 bact. per community	ES	2	0	0	2	0	4
48,412 communities	AS	14	13	0	26	2	55
<b>coA derivatives</b> (10 targets)	KS	106	0	50	17	1	174
5 bact. per community	ES	0	0	0	0	1	1
95,256 communities	AS	106	0	50	17	0	173
<b>lipids</b> (28 targets)	KS	3	140	22	20	0	185
7 bact. per community	ES	3	0	0	1	0	4
58,520 communities	AS	0	140	22	19	0	181
<b>sugar derivatives</b> (58 targets)	KS	11	30	78	23	0	142
11 bact. per community	ES	5	0	0	0	0	5
7,860,528 communities	AS	6	30	78	23	0	137

Table 1: Enumeration of minimal communities and their phyla composition for groups of target metabolites. KS = keystone species, ES = essential symbionts, AS = alternative symbionts

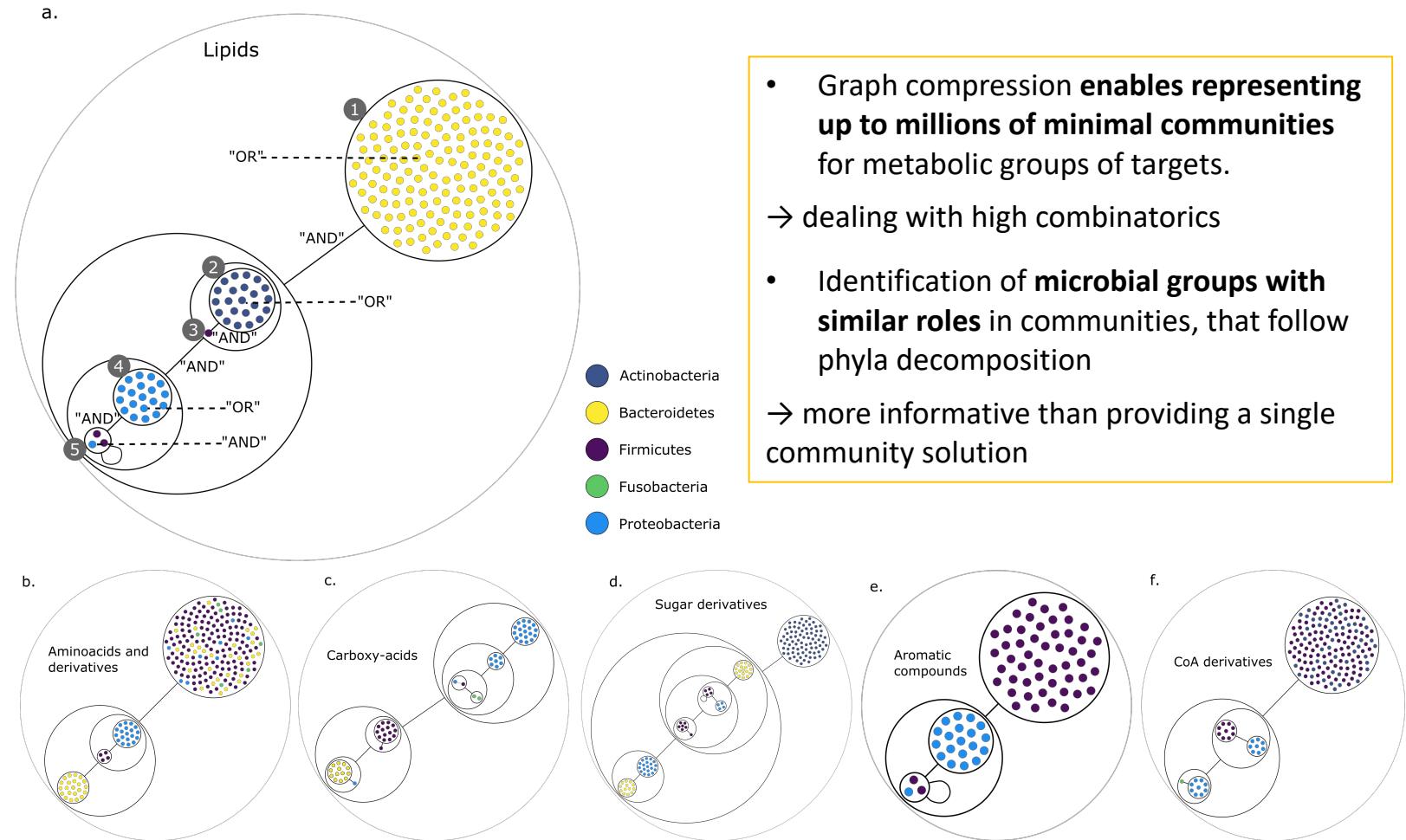


Fig. 4: Power graph analysis (graph compression) of the association of genomes in the predicted communities, coloured by phylum. In the non-compressed graphs, two nodes (microbes) were linked if they were found together in at least one minimal community.