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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**

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



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



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

Workflow

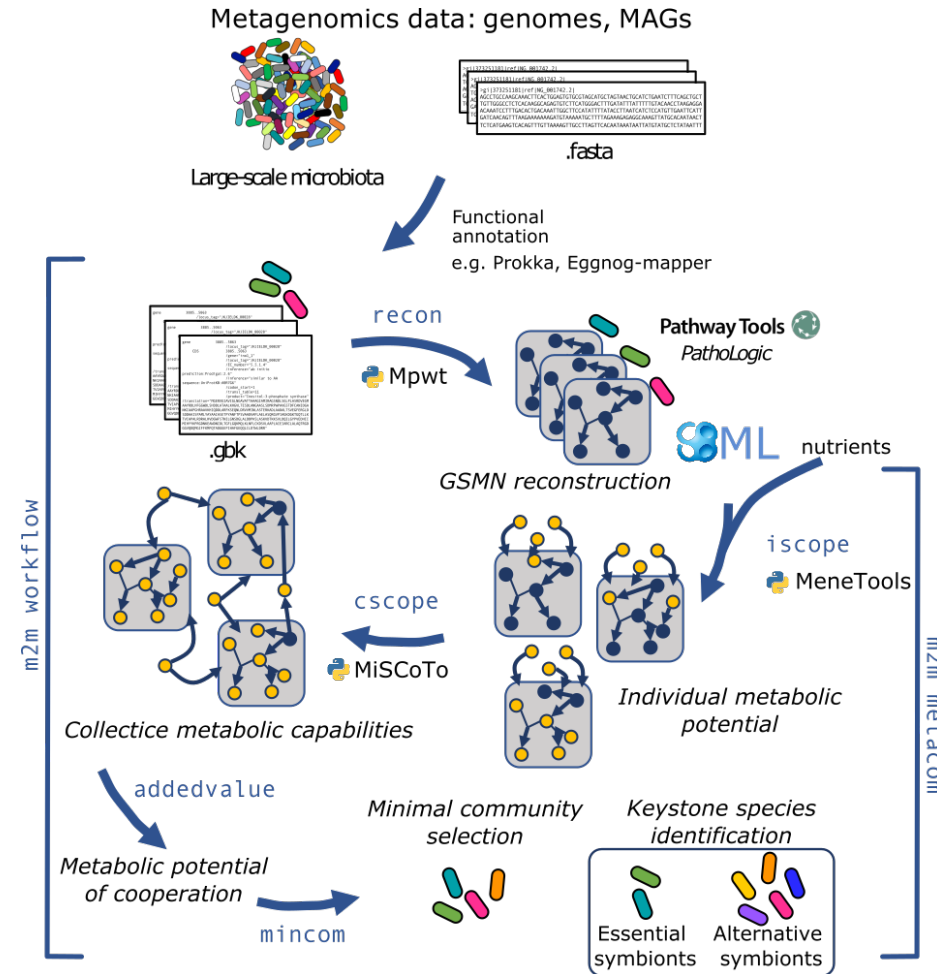
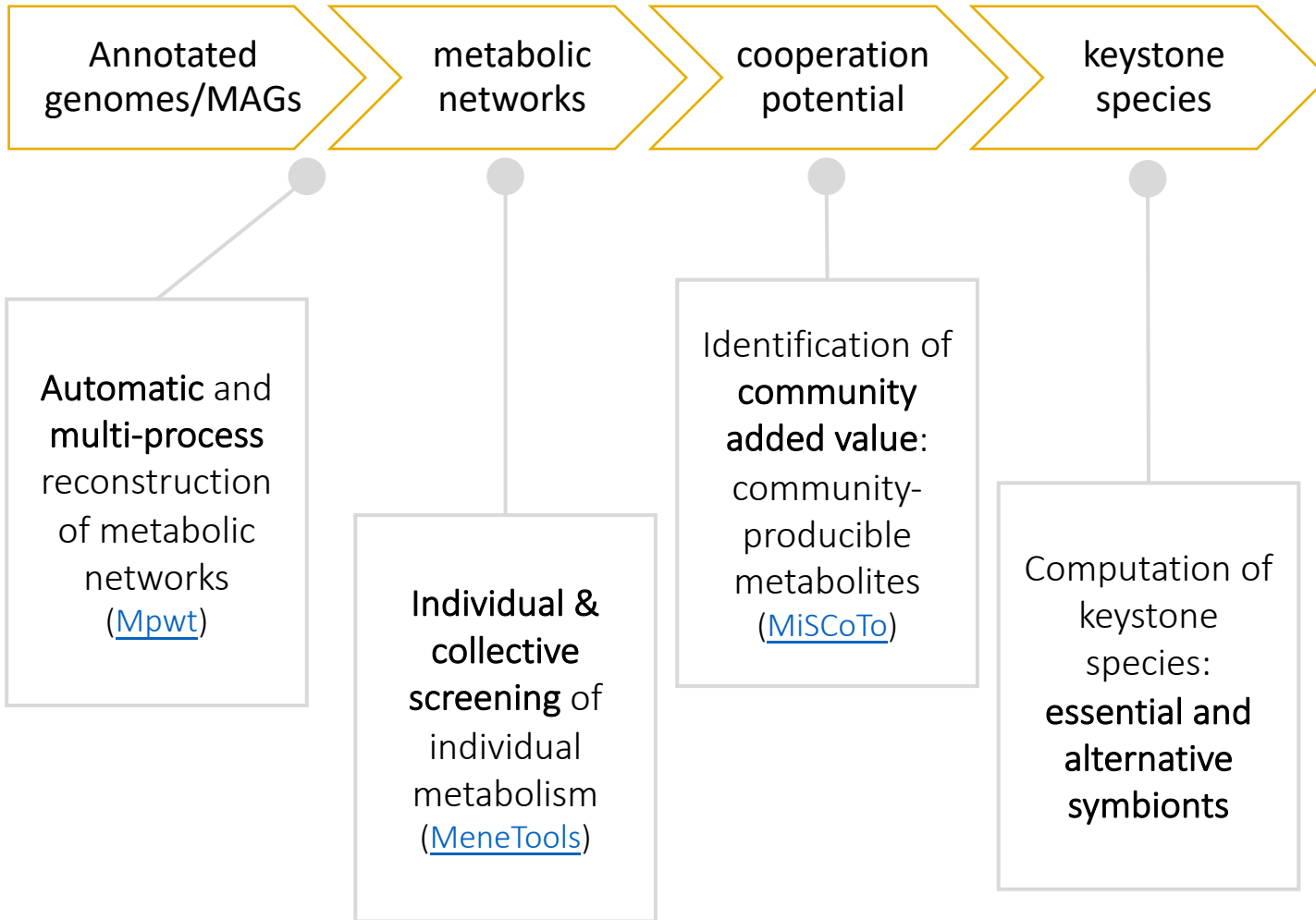


Fig. 1: flexibility of m2m's global workflow. The metacom command can run the workflow using existing metabolic networks (SBML)

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

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)

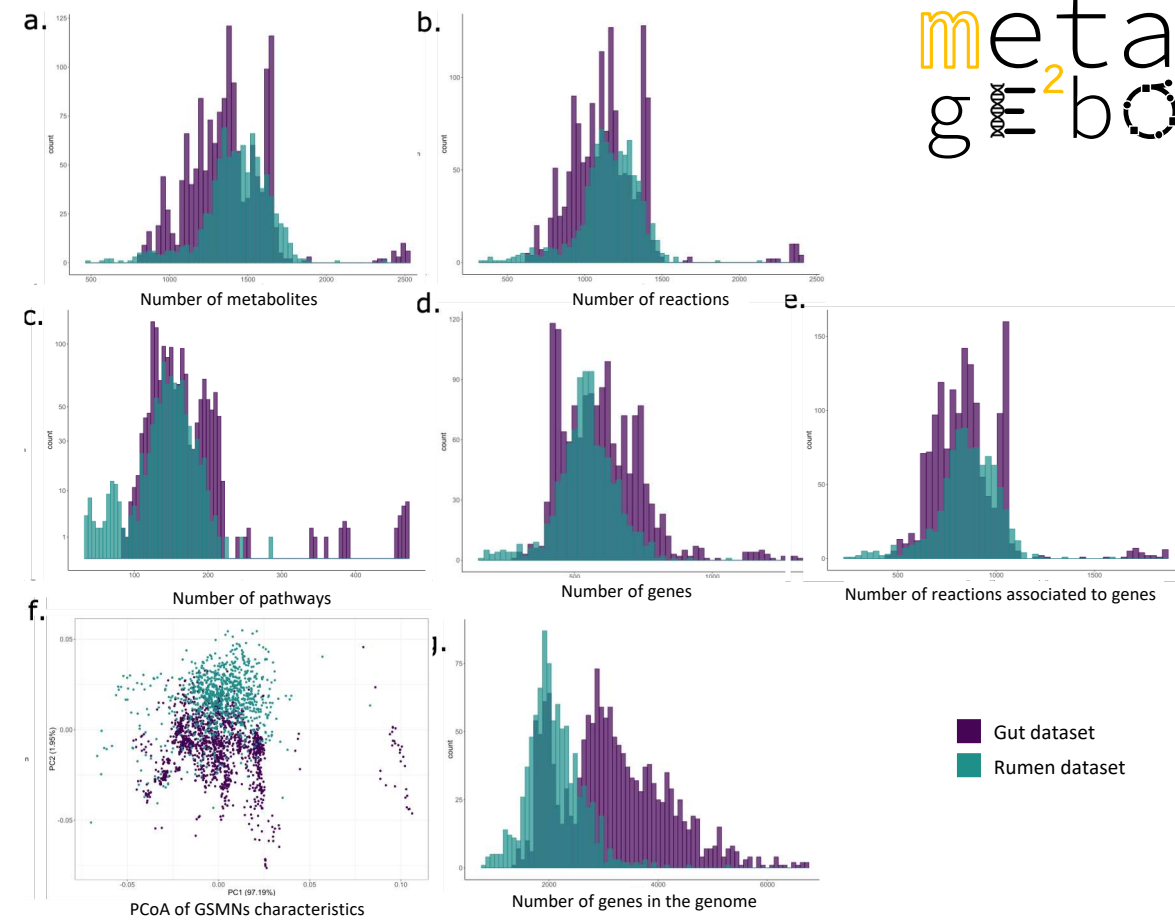


Fig. 2: Comparison of GSMNs from both datasets

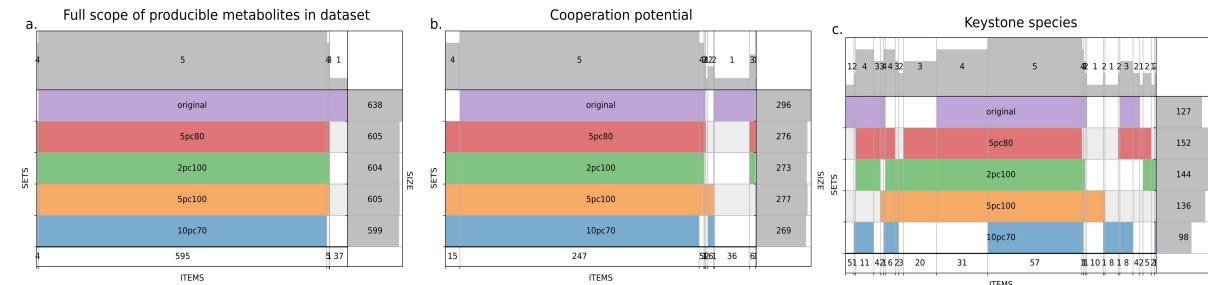


Fig. 3: Robustness analysis following MAGs degradation for the rumen dataset (upper row: original genomes, up to down: increasing genome degradation)

Analysis of gut communities

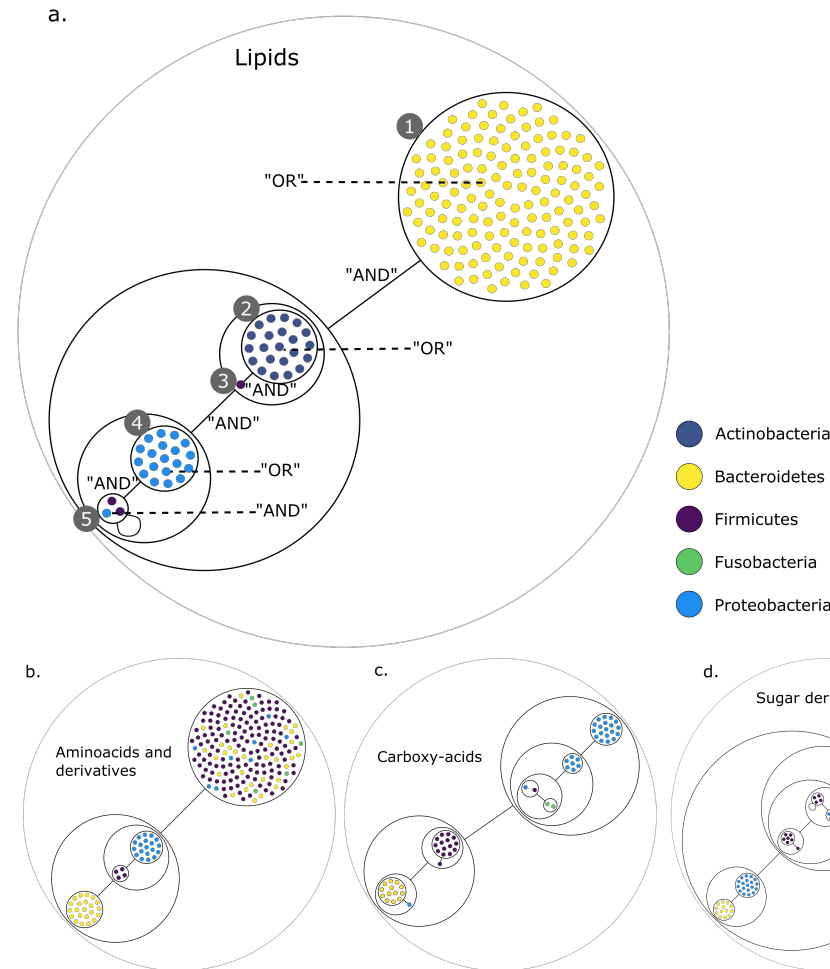
Collection of genomes = 1520 draft bacterial reference genomes ([Zou et al 2019](#))

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
all (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
aminoacids and derivatives (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
aromatic compounds (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
carboxyacids (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
coA derivatives (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
lipids (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
sugar derivatives (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



- Graph compression **enables representing up to millions of minimal communities** for metabolic groups of targets.
→ dealing with high combinatorics
- Identification of **microbial groups with similar roles** in communities, that follow phyla decomposition
→ more informative than providing a single community solution

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.