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Assessment of metabolic complementarity in large-scale microbiotas for the identification of key species

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Context

- Microbiota analyses through **metagenomic sequencing** lead to huge resources of data in order to determine the organisation of microbial communities.
- Understanding the **interactions within communities** entails the identification of functions carried out by microbes as well as the redundancy of and complementarity between these functions.
- Genome-scale metabolic network (GSMN)** reconstruction is validated method to model and simulate organisms' functions

➔ How to efficiently **screen the metabolic functions and metabolic complementarity** in hundreds or thousands of species?

➔ How to identify **key species and minimal communities** associated to functions of interest?



TOOLS AND RESOURCES



Metage2Metabo, microbiota-scale metabolic complementarity for the identification of key species

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Metage2metabo (M2M)

A flexible software resource [1] for:

- Metabolic network reconstruction**
- Modelling of **individual and collective metabolic capabilities**
- Identification of the **cooperation potential** within a community
- Community reduction and identification of key species** with respect to a metabolic objective

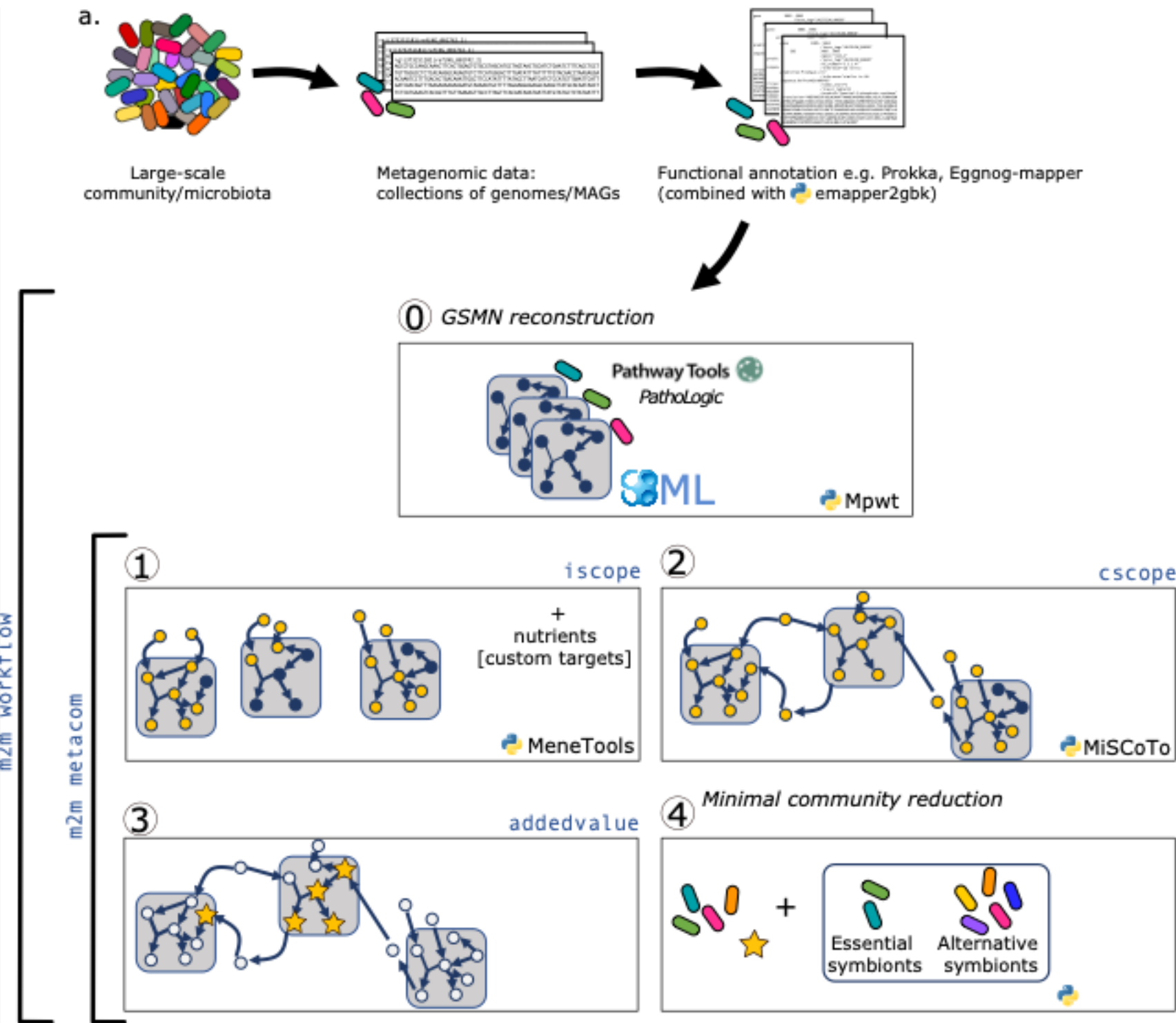
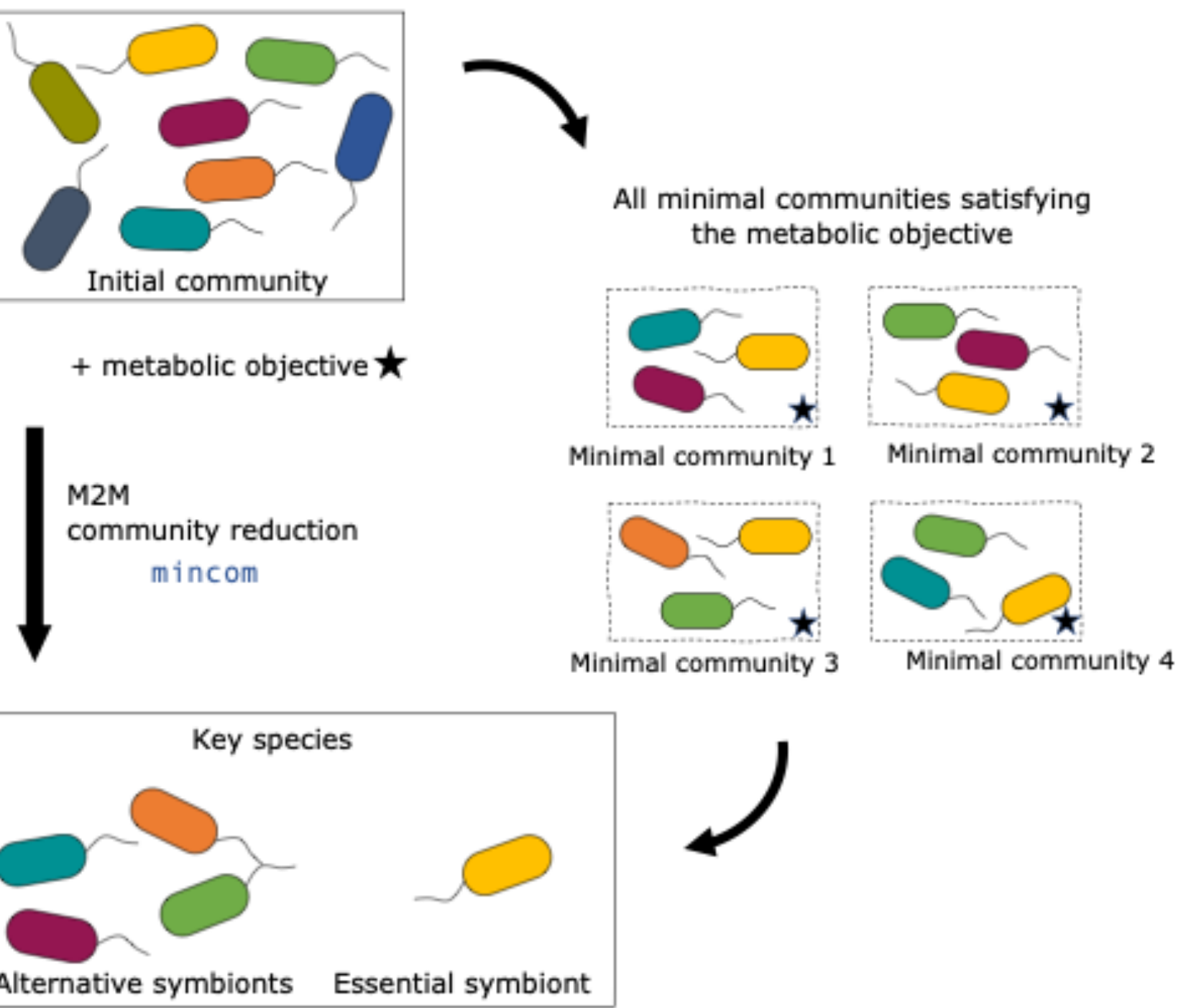


Fig 1: M2M pipeline and main functionalities.

Fig 2: Definition of **key species (KS)**. Reducing the complexity of a large community can help understand the mechanisms and interactions associated to functions. Yet, up to millions of equivalent minimal communities can exist for a given metabolic objective. KS consist in all species occurring in at least one minimal community. They can be further distinguished in **essential symbionts** (occurring in all minimal communities) and **alternative symbionts**.

Suitability of metabolic modelling to MAGs

- 913 Metagenome Assembled Genomes (MAGs) of the cow rumen microbiota [2] were **randomly degraded**: removal of 2% of genes, 5% of genes in 80% or 100% of MAGs, removal of 10% of genes in 70% of genomes.
- GSMNs characteristics are comparable** to those of GSMNs obtained with reference genomes.
- M2M analyses on metabolic potential of associated GSMNs, cooperation potential, community reduction and key species show a **stability of the predictions to moderate degradations of genomes**.

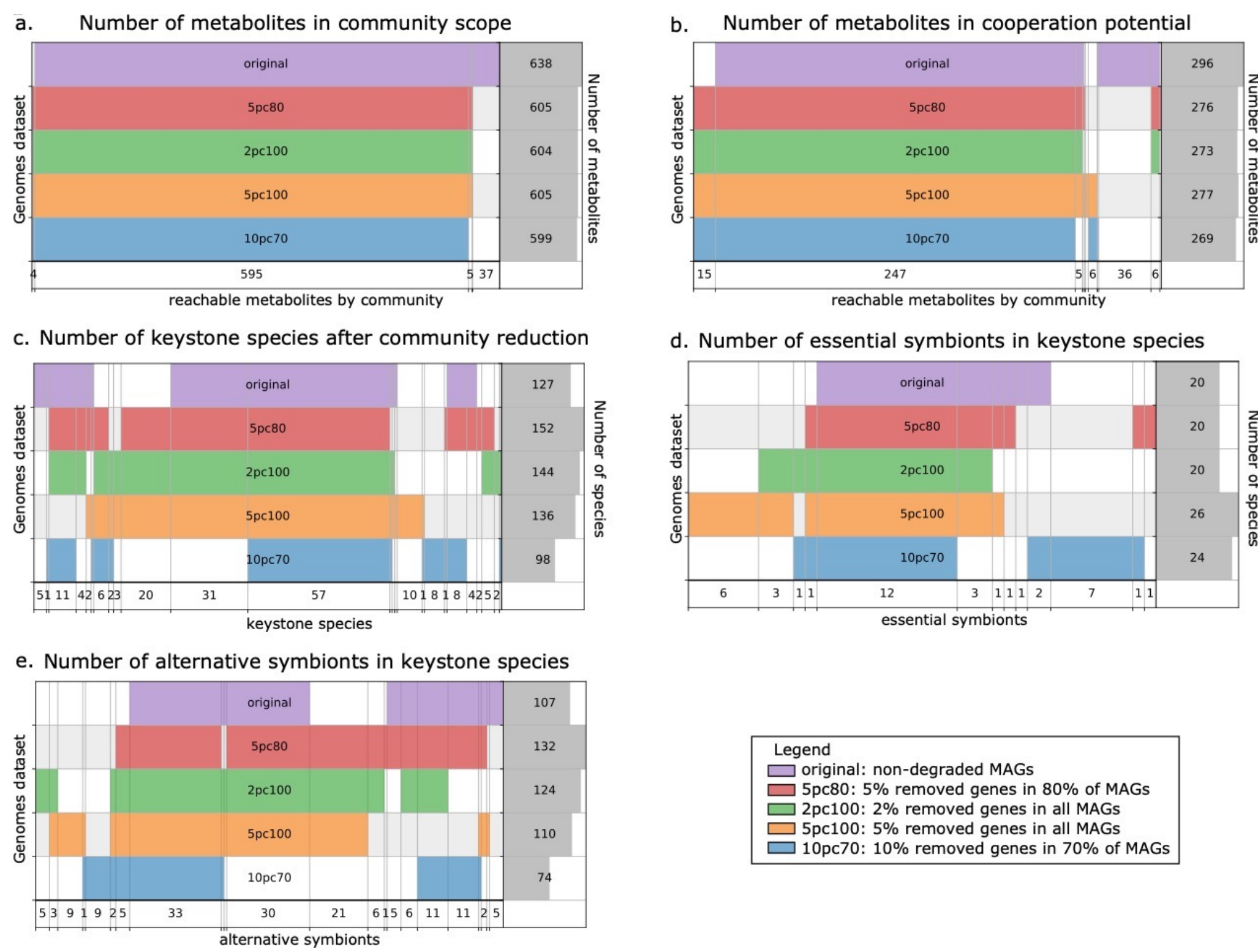


Fig 3: Comparison of the outputs of M2M for various degradations of MAGs in a set of 913 rumen MAGs from [2].

Application to 1,520 reference genomes of the gut microbiota

- 1,520 reference genomes **from culturable bacteria of the human gut microbiota** [3] → 1,520 GSMNs to be compared and analysed
- Identification of key species (KS) within the 1,520 GSMNs for **groups of metabolic end-products** (lipids, carbohydrates...)
- Enumeration** of minimal communities associated to these metabolites
- Analysis of **associations between KS within reduced communities**: identifications of bacterial groups with **equivalent roles** in the community with respect to the metabolic end-products.

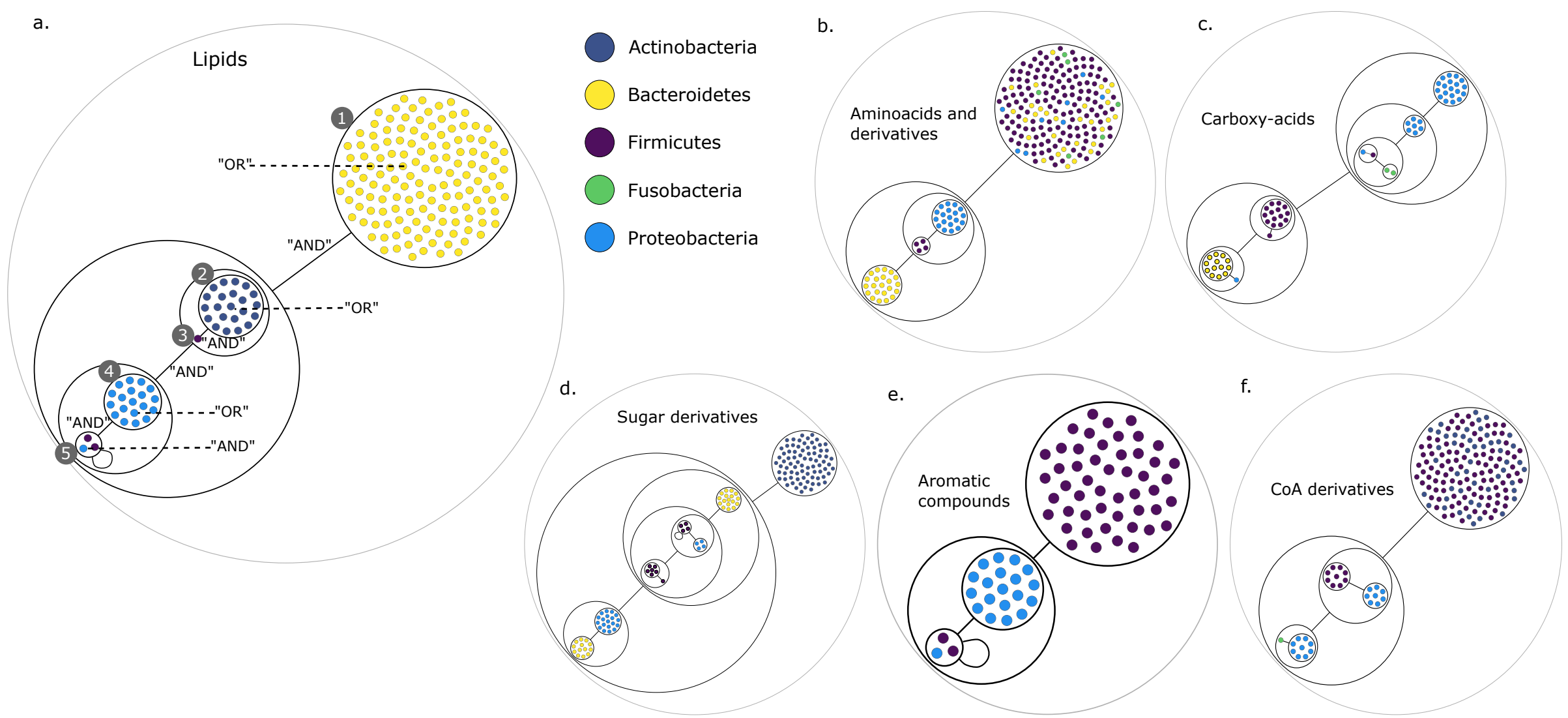


Fig 4: Analysis of the **association between species in minimal communities** associated to groups of metabolites. Power graphs depict the association of KS within all enumerated minimal communities. Nodes (species) are coloured based on their phylum. (a) illustrates how to read the composition of any community among the 58,520 equivalent minimal communities suitable for lipids producibility (see Table 1).

		Firm.	Bact.	Acti.	Prot.	Fuso.	total
aminoacids and derivatives (5 targets)	KS	142	52	0	27	6	227
	ES	0	0	0	0	0	0
aromatic compounds (11 targets)	KS	142	52	0	27	6	227
	ES	2	0	0	1	0	3
carboxyacids (14 targets)	KS	16	13	0	28	2	59
	ES	2	0	0	2	0	4
coA derivatives (10 targets)	KS	106	0	50	17	1	174
	ES	0	0	0	0	1	1
lipids (28 targets)	KS	3	140	22	20	0	185
	ES	3	0	0	1	0	4
sugar derivatives (58 targets)	KS	11	30	78	23	0	142
	ES	5	0	0	0	0	5
	AS	6	30	78	23	0	137

Table 1: **Community reduction analysis of the metabolite categories in the gut**. All minimal communities were enumerated, starting from the set of 1,520 GSMNs with respect to sets of target metabolites. KS: key species, ES: essential symbionts, AS: alternative symbionts, Firm.: Firmicutes, Bact.: Bacteroidetes, Acti.: Actinobacteria, Prot.: Proteobacteria, Fuso.: Fusobacteria.

Discussion

- Modelling is **qualitative**, using the network expansion algorithm [4]: robustness to data imprecision despite a loss in quantitative predictions.
- M2M pinpoints **mutualistic metabolic interactions** within large communities of bacteria
- Application to **metagenomic samples**: 1 sample = 1 community. Illustrated on the MetaHIT dataset [5] in [1].
- M2M can help **identifying cornerstone taxa** in microbiomes.

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