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Analyzing and modelling functions carried by key species in minimal microbial communities

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From Genome-Scale Metabolic Network to Metabolic potentials

Hundreds of **bacteria species** colonize the **human gut**.

Interaction in microbiota: competition or **cooperation**.

Metabolic modelling:

- Genome-scale metabolic Networks (GSMNs) [1]
- Producibility modelling: network expansion [2]

Community **metabolic potential**:

- **Individual scope**.
- **Production of new metabolites** through metabolic exchanges.
→ By **whom** and **how**?

Minimal community selection:

- **Metage2Metabo** (M2M) [3] **model** the interactions.

Minimal communities for six families of compounds as targets

Community initial: 1,500 bacteria [3]

		TOTAL
Aminoacids and derivatives (5 targets)	KS	227
4 bact. per community	ES	0
120,329 communities	AS	227
Aromatic compounds (11 targets)	KS	72
5 bact. per community	ES	3
950 communities	AS	69
Carboxyacids (14 targets)	KS	59
9 bact. per community	ES	4
48,412 communities	AS	55
CoA derivatives (10 targets)	KS	174
5 bact. per community	ES	1
95,256 communities	AS	173
Lipids (28 targets)	KS	185
7 bact. per community	ES	4
58,520 communities	AS	181
Sugar derivatives (58 targets)	KS	142
11 bact. per community	ES	5
7,860,528 communities	AS	137

Key Species (KS):

Species occurring at least in **one minimal community**

Essential Symbionts (ES):

Species occurring in **all minimal communities**

Alternative Symbionts (AS):

Species occurring in **some minimal communities**

Logic Programming

ASP

Answer Set Programming [4]

Declarative programming paradigm.

Solve **combinatorial** problems with knowledge.

Knowledge

```
bacteria("B1").
metabolite("M_S1_c", "S1", "B1").
metabolite("M_S2_c", "S2", "B1").
metabolite("M_A_c", "A", "B1").
metabolite("M_B_c", "B", "B1").
reaction("R1", "B1").
reactant("M_S1_c", "R1", "B1").
reactant("M_S2_c", "R1", "B1").
product("M_A_c", "R1", "B1").
reaction("R2", "B1").
reactant("M_A_c", "R2", "B1").
reactant("M_B_c", "R2", "B1").
product("M_B_c", "R2", "B1").
seed("S1").
seed("S2").
```

Set of rules with two parts:

HEAD :- BODY

Head is true

if all element of body is true

```
iscope(M,S,B) :- seed(M), species(M,S,_), bacteria(B).
iscope(M,S,B) :- bacteria(B), product(M,R,B),
reaction(R,B), metabolite(M,N,B),
iscope(M2,N2,B) : reactant(M2,R,B).
```

Rules to verify hypotheses:

Unique metabolite

A metabolite produced by **all bacteria of a group**, and **not other bacteria of minimal communities**.

Unique reaction

A reaction activated by **all bacteria of a group**, and **not by any other bacteria of community**.

Unique metareact

A **unique metabolite** produced by **unique reaction** carried by **all bacteria of a group** and **not by others**.

Power graph compression method

Up to millions of possible **minimal communities** for a set of targets.

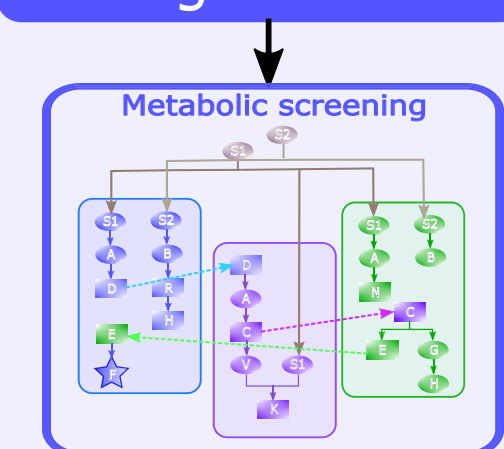
How **visualize** them ?

- Association graph
→ Not easily readable on thousands minimal communities.

- **Graph compression**
→ shows **groups of equivalence**.

From Metage2Metabo to PowerFun

Metage2Metabo



PowerFun is an extension of the M2M study.

Groups of equivalence have been identified with power graphs.

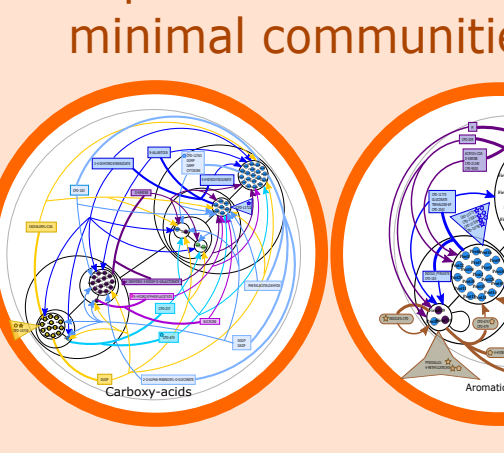
Why are the bacteria gathered together ? **Which functions are carried by the group?**

Hypotheses:

- **Unique metabolite produced**
- **Unique reaction activated**
- **Unique metareact**

PowerFun

Explainable models of minimal communities



PowerFun Results

Groups carry:

- Unique metabolites
- Unique reactions
- Unique metareact
- Can be 2 reactions for 1 metabolite

Also:

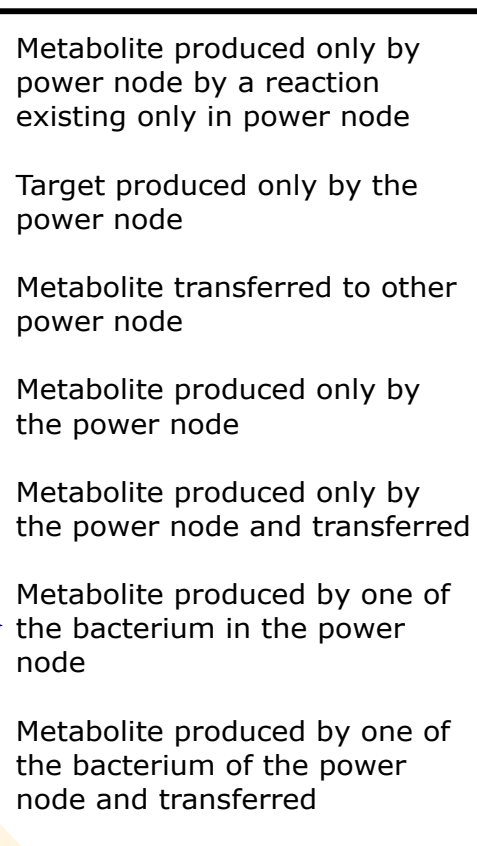
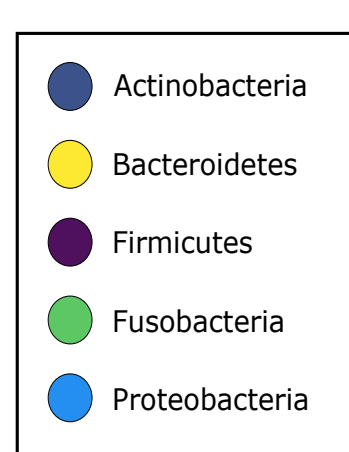
- Some unique metabolites **transferred to all nodes**
- Some unique metabolites are **targets**
- Some power nodes are **not explained** (C)

Numbers for Lipids set of targets:

- 1,800 transfers
- 85 unique reactions
→ 24 activated
- 209 unique metabolites
→ 138 carried by blue node (D)
- 54 unique metareact
→ 16 activated

Perspectives

- Define **new rules** for non-explained power nodes
- **Constrain** definition of **exchanged** metabolites
→ Is it involved in chained reactions to produce targets?



¹ K. C. H. van der Ark, R. G. A. van Heek, V. A. P. Martins Dos Santos, C. Belzer, and W. M. de Vos. "More than just a gut feeling: constraint-based genome-scale metabolic models for predicting functions of human intestinal microbes," Microbiome, vol. 5, no. 1, BioMed Central, p. 78, Jul. 14, 2017. doi: 10.1186/s40168-017-0299-x.

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