



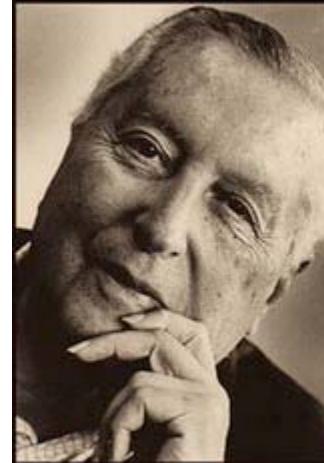
Philippe Vandenkoornhuyse

Modeling of interactions between microorganisms by analysing the meta-metabolism network



Université de Rennes I
Campus de Beaulieu
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UMR6553 EcoBio,
Rennes, France

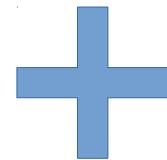
Ilya Prigogine



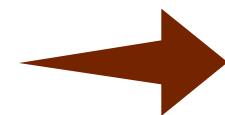
The irreversibility of time is the mechanism that brings order out of chaos.

(Ilya Prigogine)

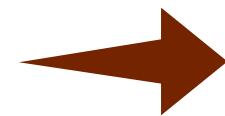
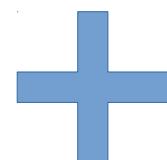
"This is indeed an essential part of the scientific revolution we are witnessing at the end of the 20th century. Science is a dialogue with nature. In the past this dialogue has taken many forms. We feel that we are at the end of the period which started with Galileo, Copernicus and Newton and culminated with the discovery of quantum mechanics and relativity. This was a glorious period but in spite of all its marvelous achievements it led to an oversimplified picture of nature, a picture which neglected essential aspects. Classical science emphasized stability, order and equilibrium. Today we discover instabilities and fluctuation everywhere. Our view of nature is changing dramatically"



symbionts



Holobiont



controversial
Extended phenotype

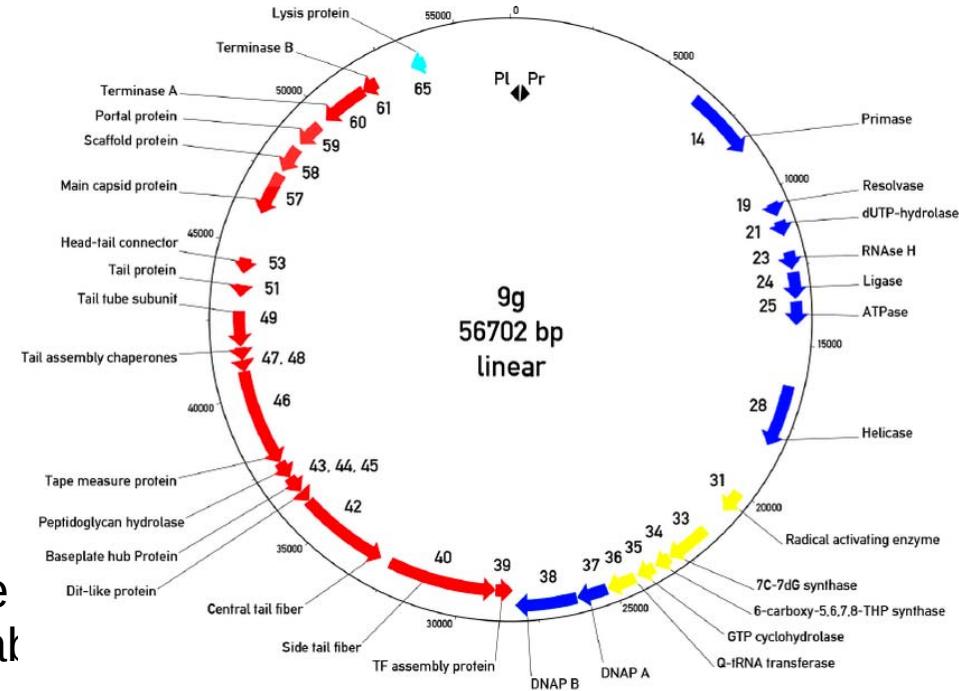
Genome =
A polymer of ATCG



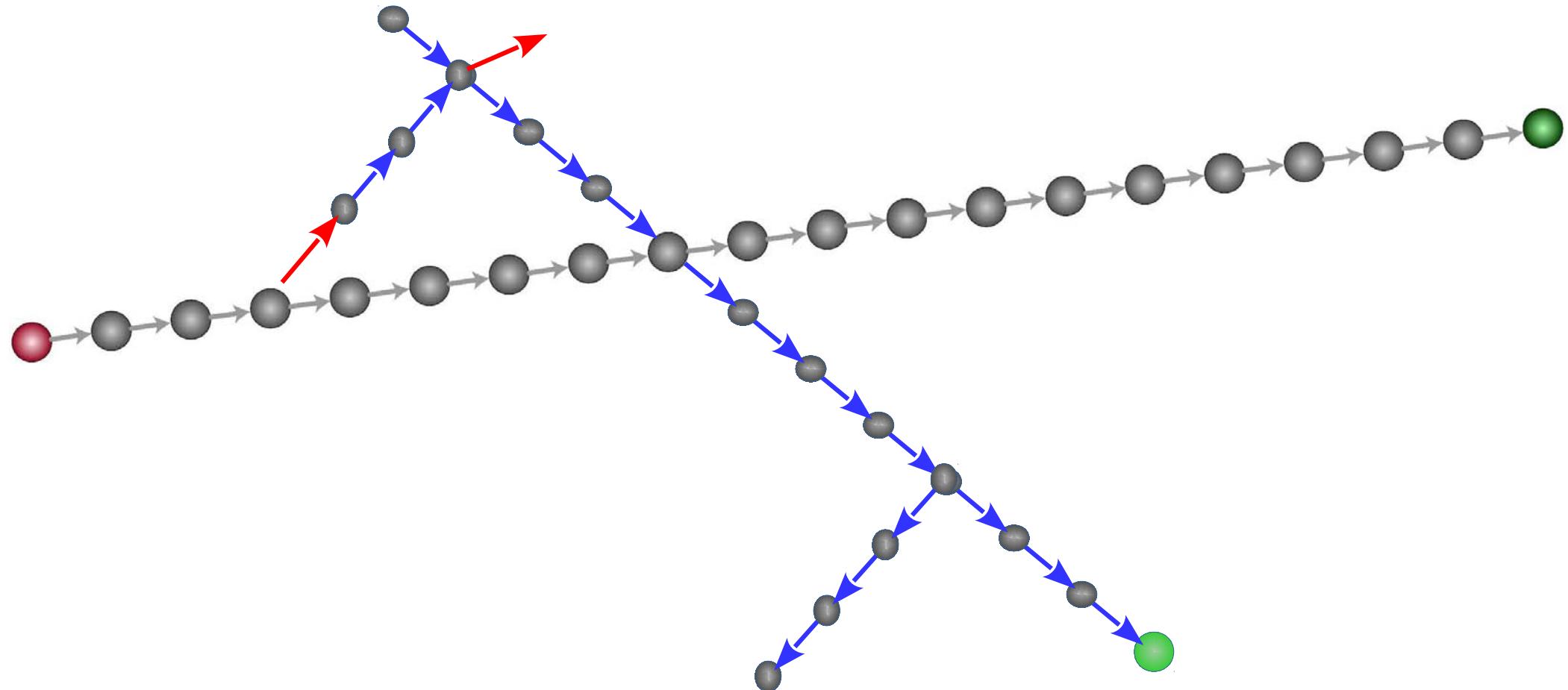
... from which genes can be predicted...
thus, a complex repository of informations (metabolism, cellular signaling, traits,...)

... thus data that can be turned into a table

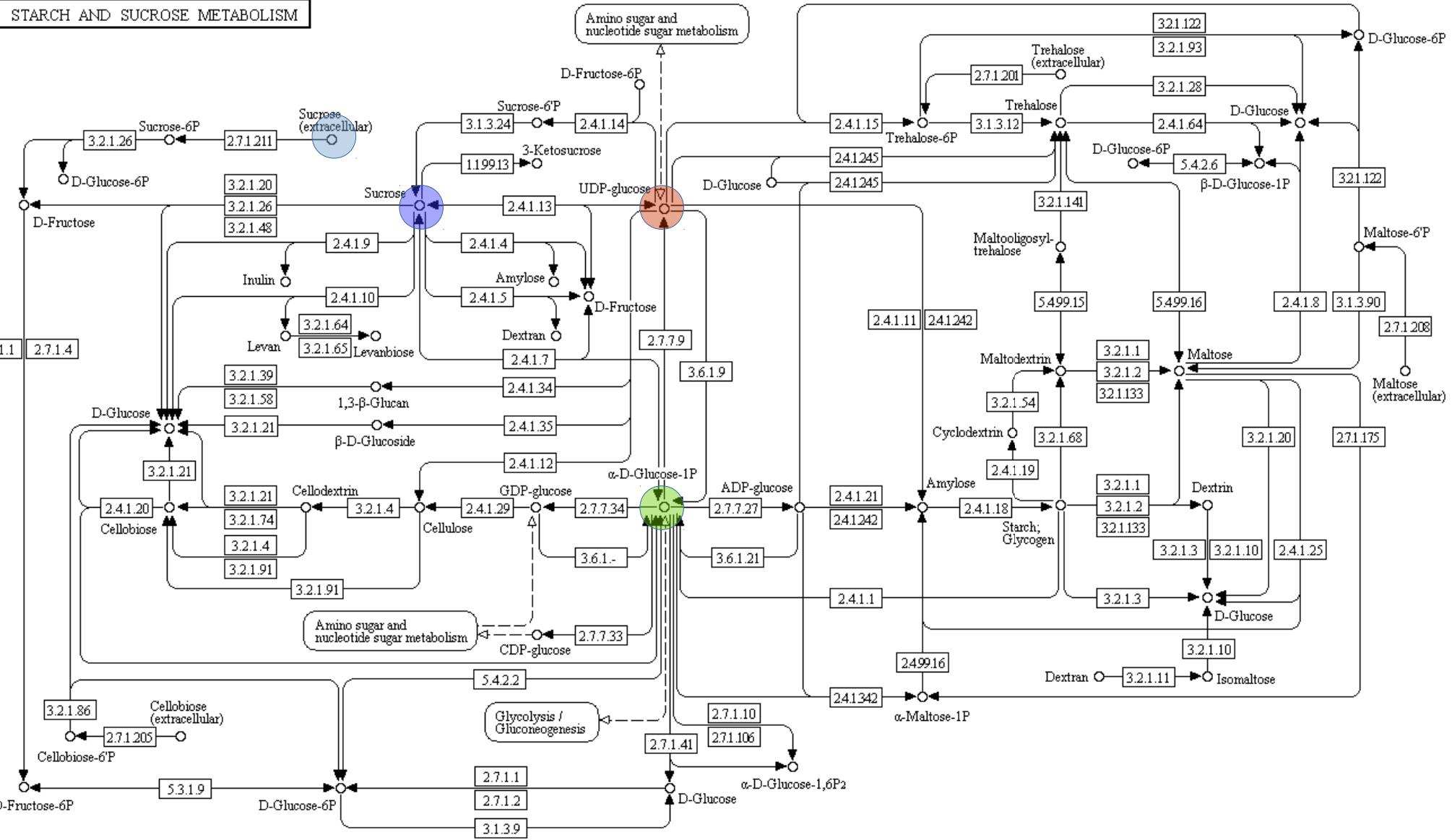
= presence/absence
comparisons to data!



From a given molecule, cascade of reactions to arrive at an end product (green)



STARCH AND SUCROSE METABOLISM



One genome :

Prediction of genes

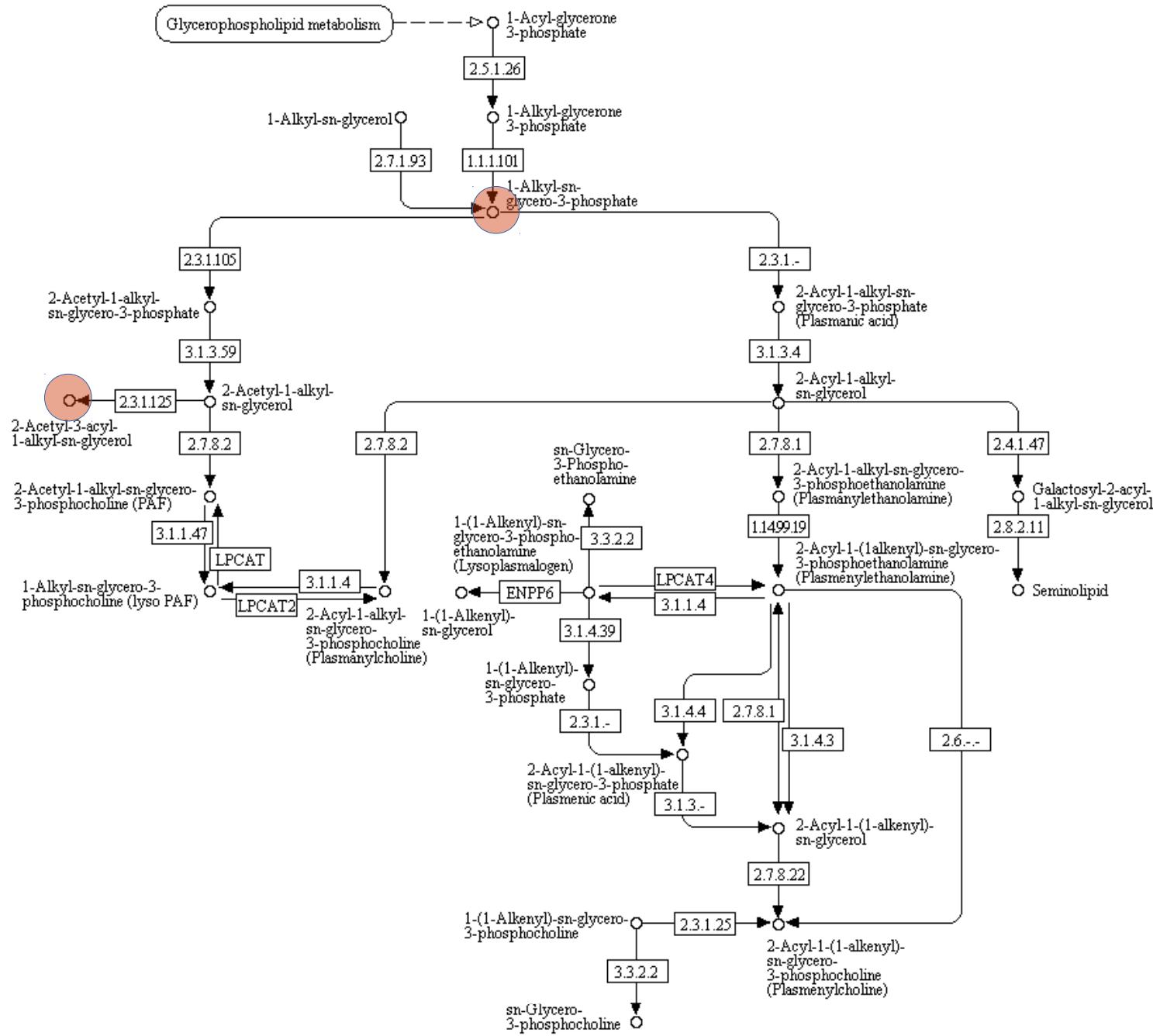
Prediction of metabolic pathways

Prediction of genome functioning from the gene repertoire

But not that straightforward !

To go from A to B product, possibility of different costs, possibility of by-pass...

ETHER LIPID METABOLISM

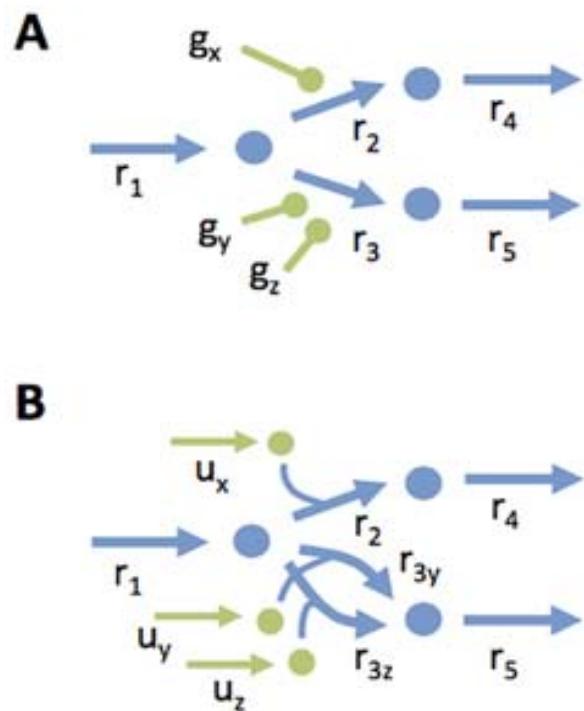


New abstractions & methods to model....

RESEARCH ARTICLE

Stoichiometric Representation of Gene–Protein–Reaction Associations Leverages Constraint-Based Analysis from Reaction to Gene-Level Phenotype Prediction

Daniel Machado^{1✉*}, Markus J. Herrgård², Isabel Rocha¹



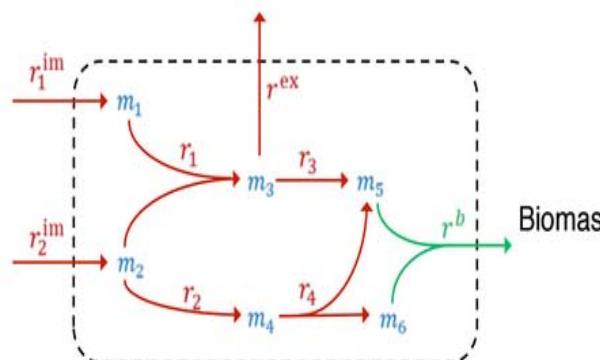
C

$$E = \begin{bmatrix} 1 & 1 \\ 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 0 & 1 \end{bmatrix} \quad \begin{array}{l} r_1 \\ r_2 \\ r_3 \\ r_4 \\ r_5 \end{array}$$
$$E' = \begin{bmatrix} 1 & 1 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \quad \begin{array}{l} r_1 \\ r_2 \\ r_{3y} \\ r_{3z} \\ r_4 \\ r_5 \end{array}$$

gene-wise support vector

$$\left[\begin{array}{l} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{array} \right] \quad \begin{array}{l} u_x \\ u_y \\ u_z \end{array}$$

Metabolic Network Definition



$$S = \begin{pmatrix} r_1 & r_2 & r_3 & r_4 & r_1^{im} & r_2^{im} & r^{ex} & r^b \\ m_1 & -1 & 0 & 0 & 1 & 0 & 0 & 0 \\ m_2 & -1 & -1 & 0 & 0 & 0 & 1 & 0 \\ m_3 & 1 & 0 & -1 & 0 & 0 & 0 & -1 \\ m_4 & 0 & 1 & 0 & -1 & 0 & 0 & 0 \\ m_5 & 0 & 0 & 1 & 1 & 0 & 0 & 0 \\ m_6 & 0 & 0 & 0 & 1 & 0 & 0 & -1 \end{pmatrix}$$

$$v = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_1^{im} \\ v_2^{im} \\ v^{ex} \\ v_b \end{pmatrix}$$

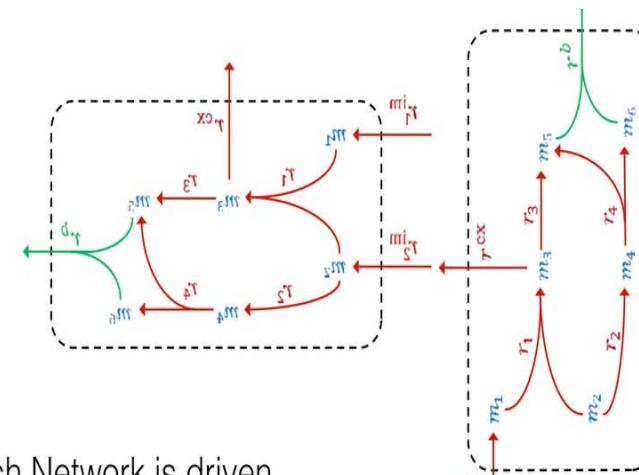
Linear program (FBA)

$$\max \quad v_b$$

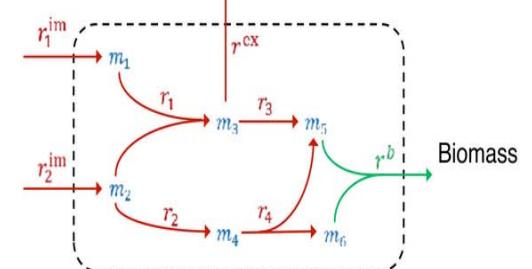
$$\text{s.t.} \quad S v = 0 \quad (1)$$

$$v_{min} \leq v \leq v_{max} \quad (2)$$

Flux Balance Analysis



Each Network is driven
by its own objective



Images: Burdinich, Bourdon &
Eveillard, 2016

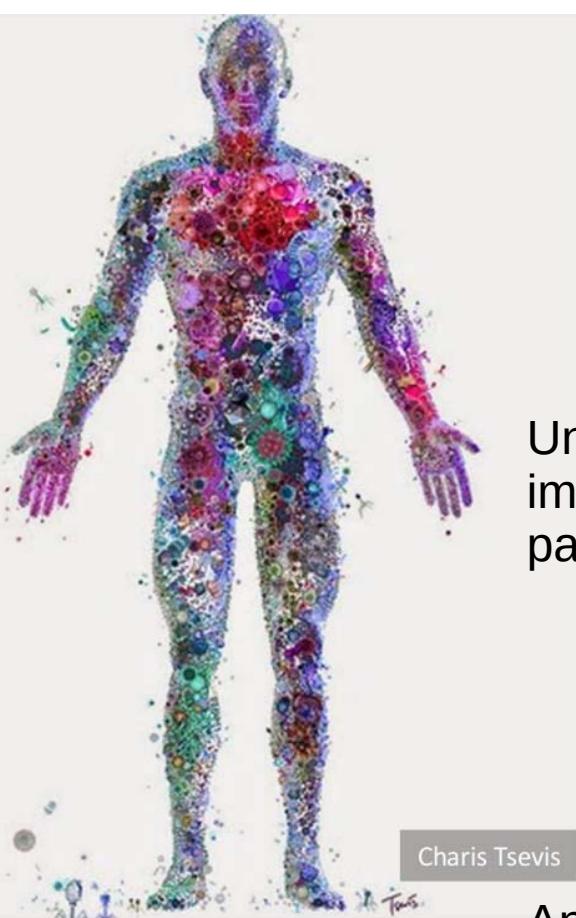


Charis Tsevis



Human :

Number of genes contained
within gut flora outnumbers that
contained within our own genome
150-fold

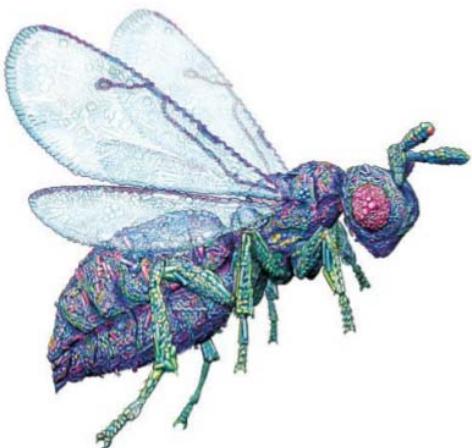


Under this framework, microbiota have to be analysed as an important part of the human body :

**We have never been individuals !
Rethinking individuality... the holobiont concept**

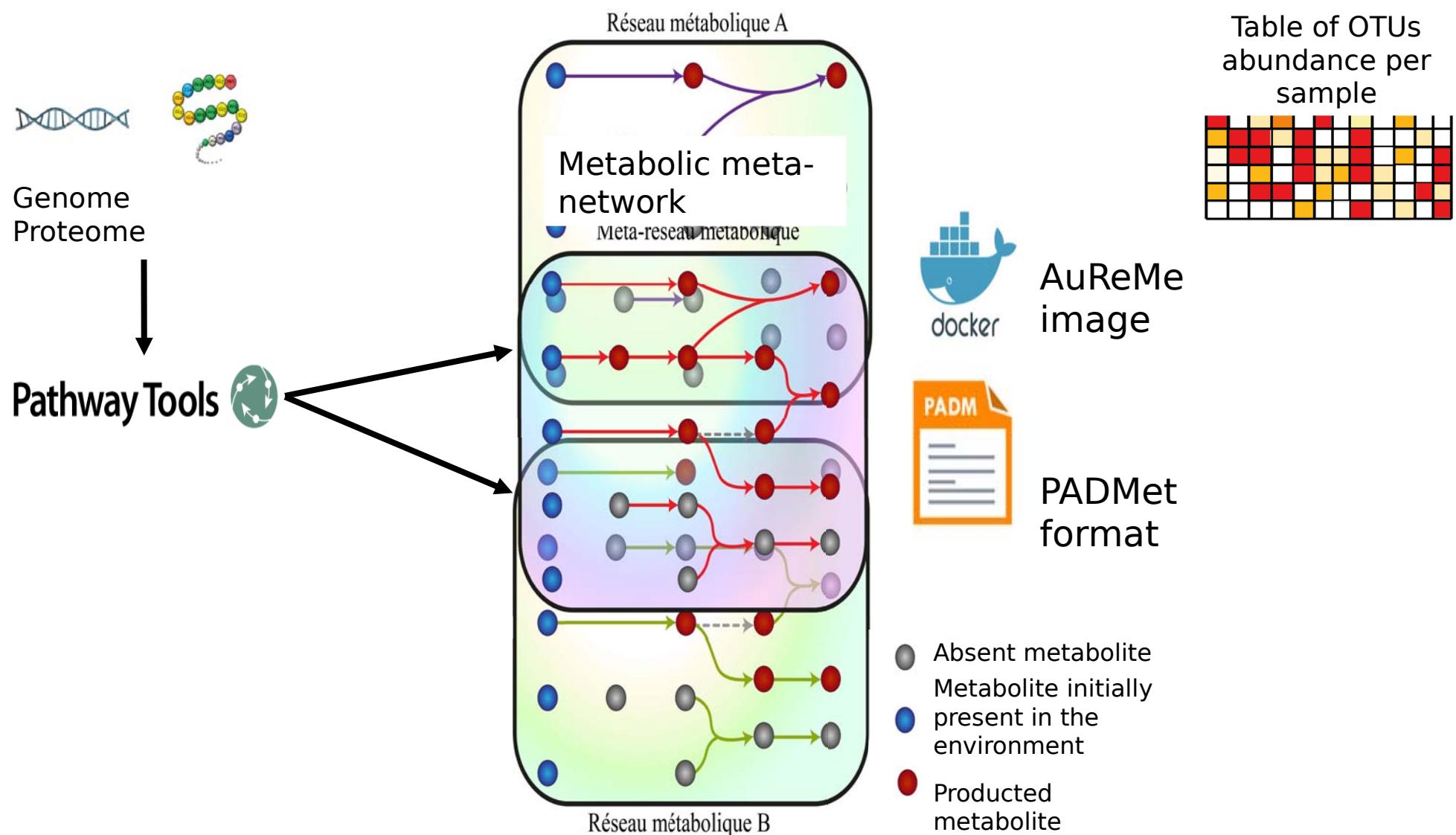
Analyses of microbiota

- complexity
- evolutionary hypotheses/theories to explain this complexity
Genomic reduction to escape competitive exclusion and stabilise
- Interactions among microorganisms



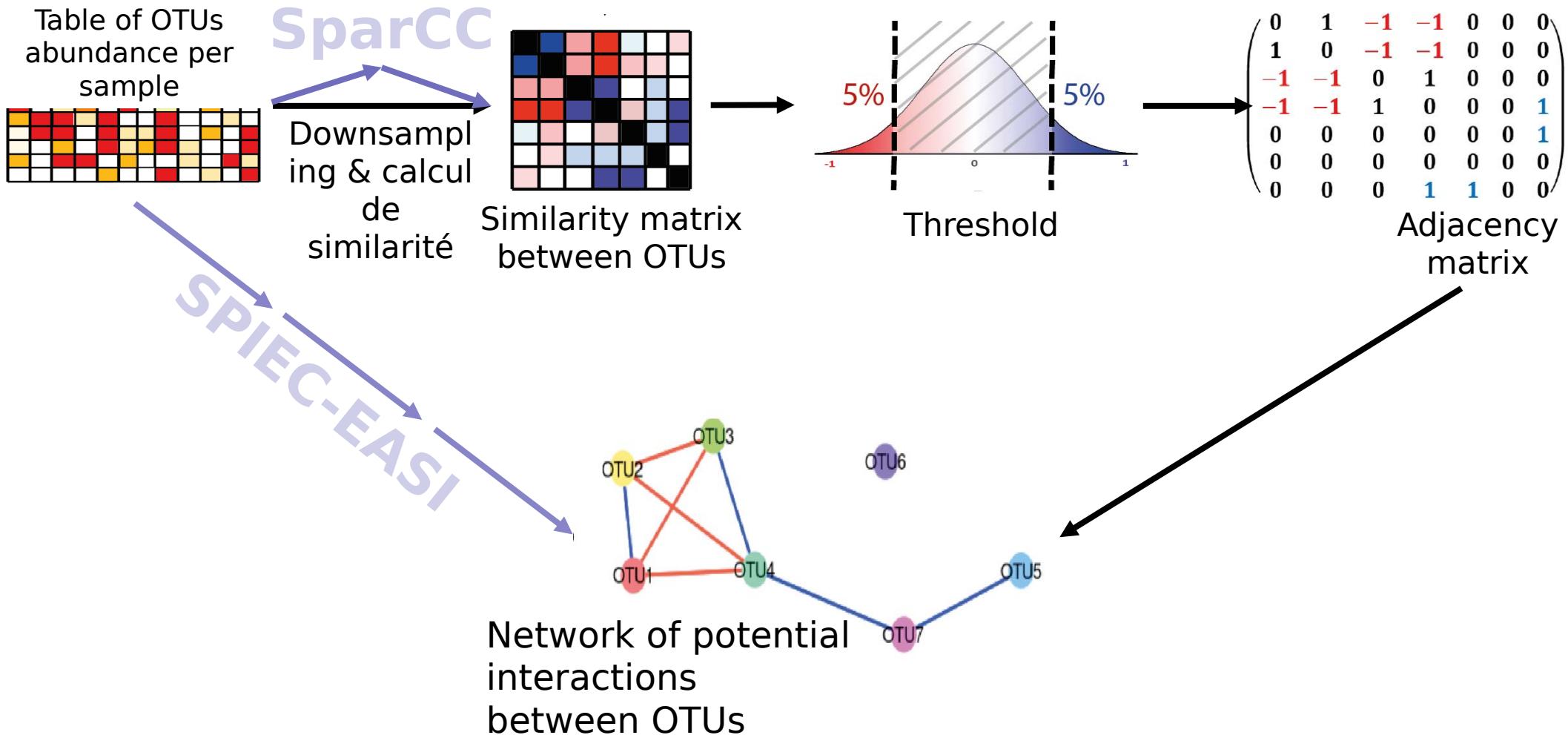
De la modélisation d'un génome à la modélisation de génomes en interaction

Reconstruction de meta-métabolismes sous l'hypothèse de complémentarités
→ la complétion métabolique (complémentation)

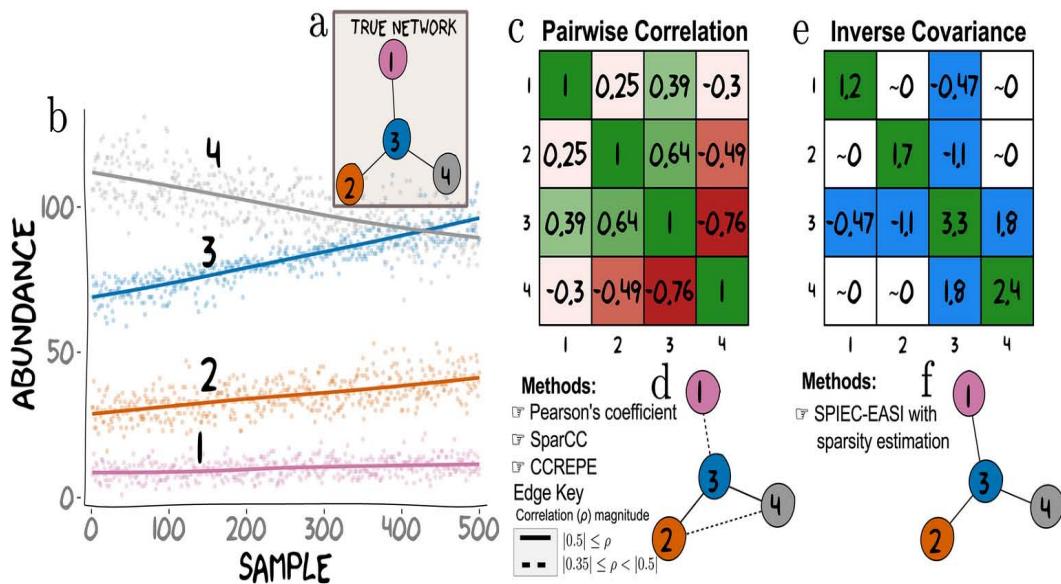


The microbiome beyond the horizon of ecological and evolutionary theory

Britt Koskella^{1*}, Lindsay J. Hall² and C. Jessica E. Metcalf^{1,3}



SparCC: Friedman & Alm, 2012
 SPIEC-EASI: Kurtz *et al.*, 2012

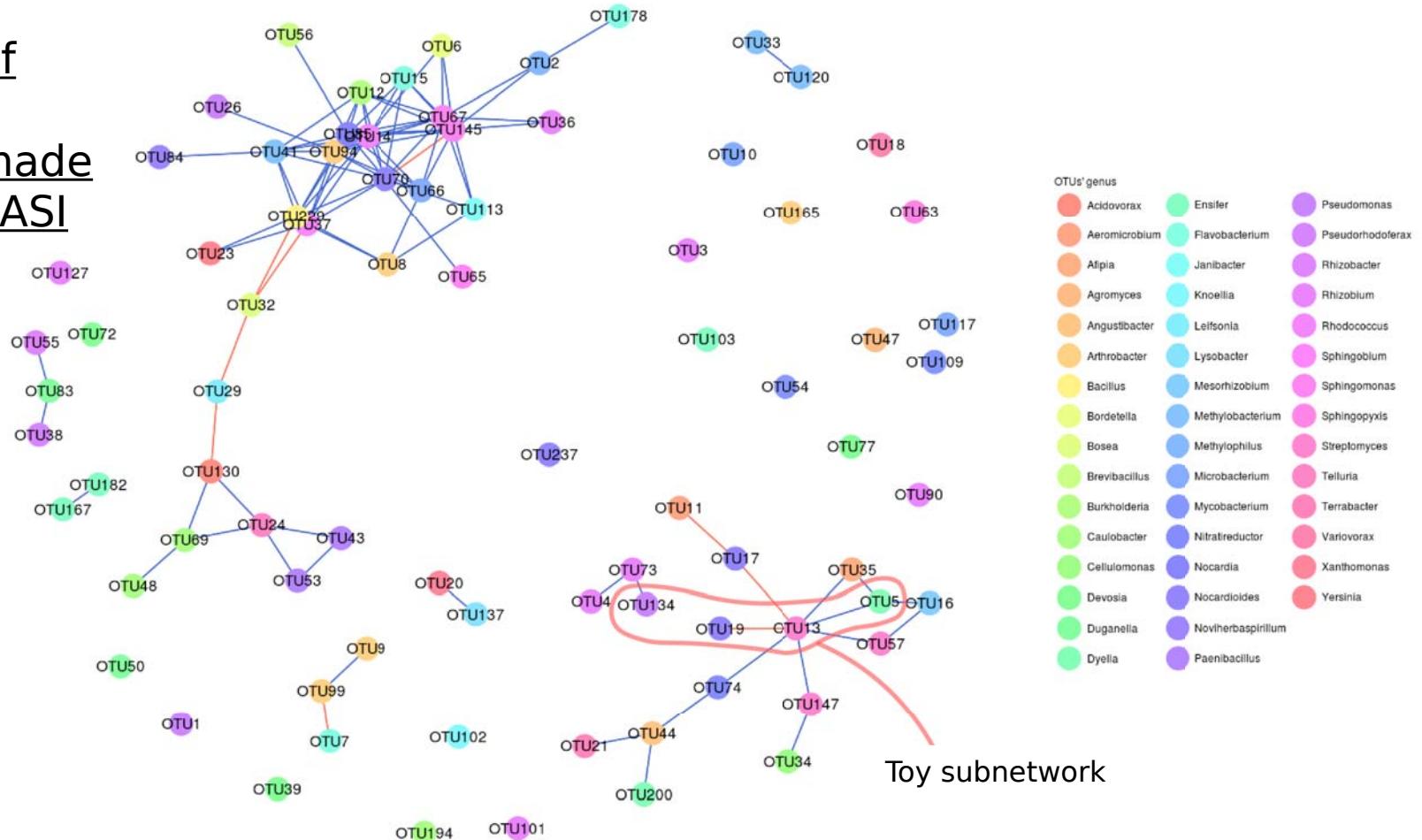


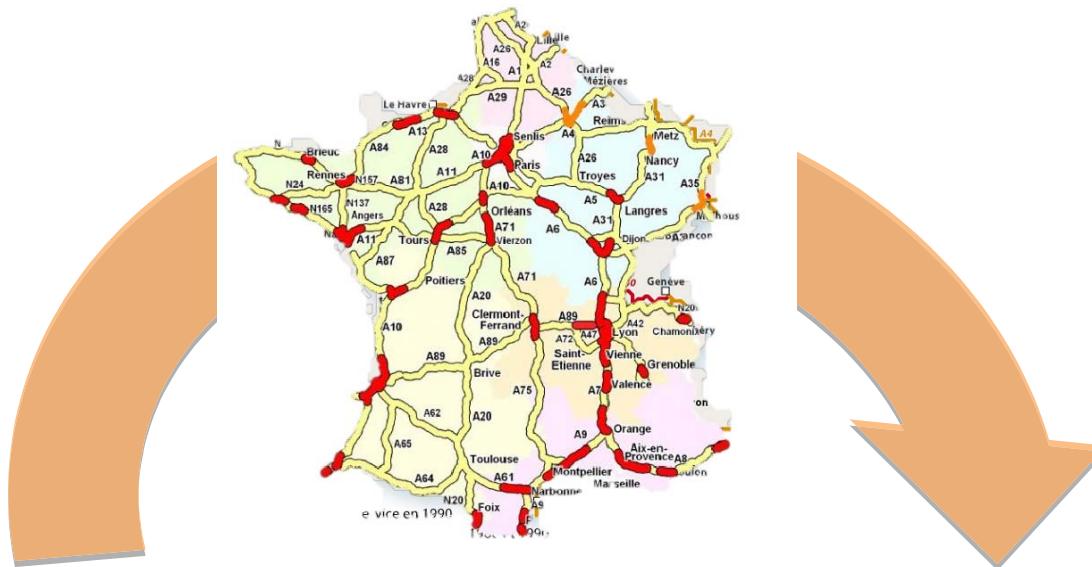
$$C^{-1} = \arg \min_{C^{-1} \in PD} -\text{logdet}(C^{-1}) + \text{tr}(C^{-1}S) + \lambda \|C^{-1}\|_1$$

Likelihood term

Sparsity term

Network of potential interactions made with SPIEC-EASI





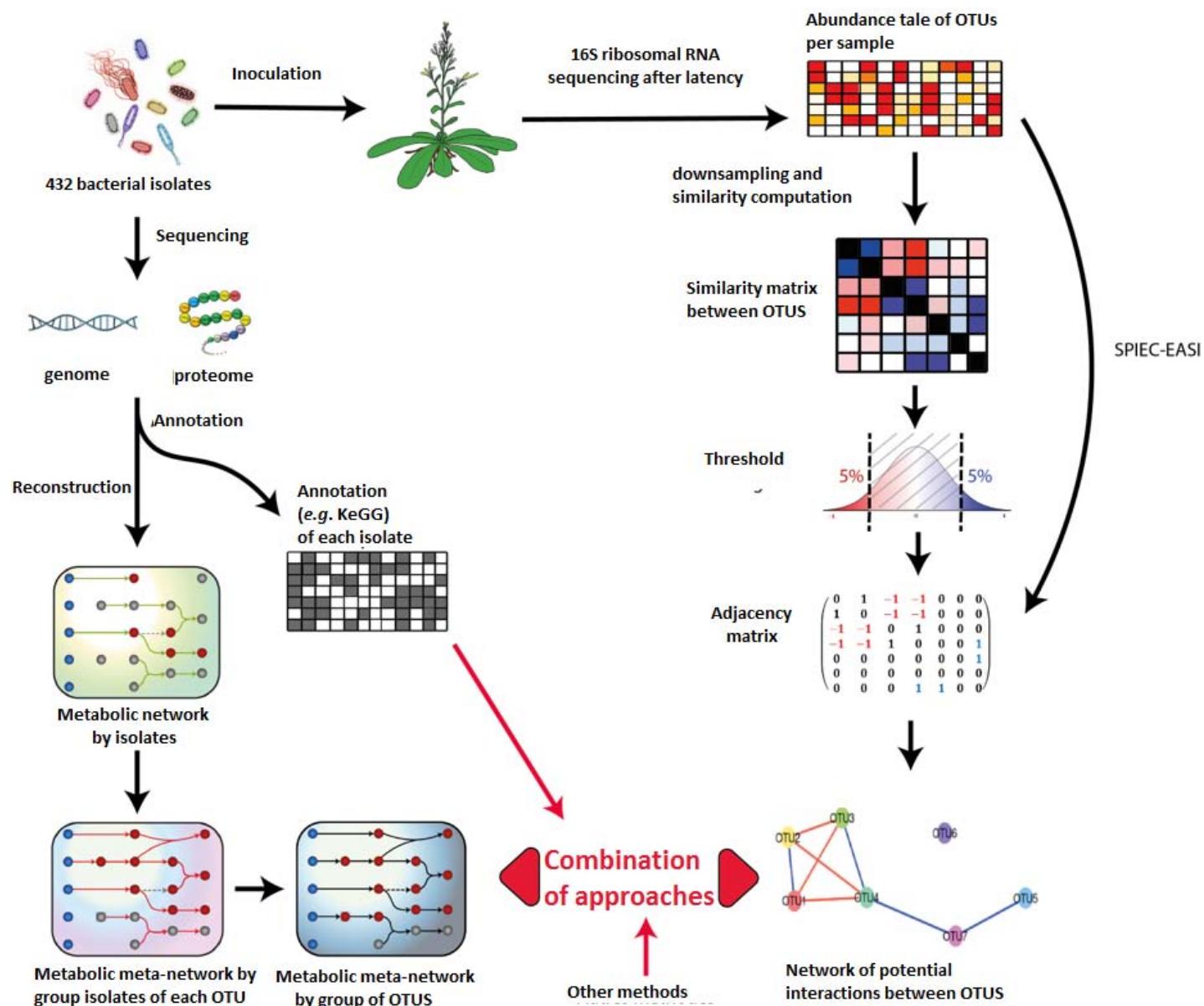
1990



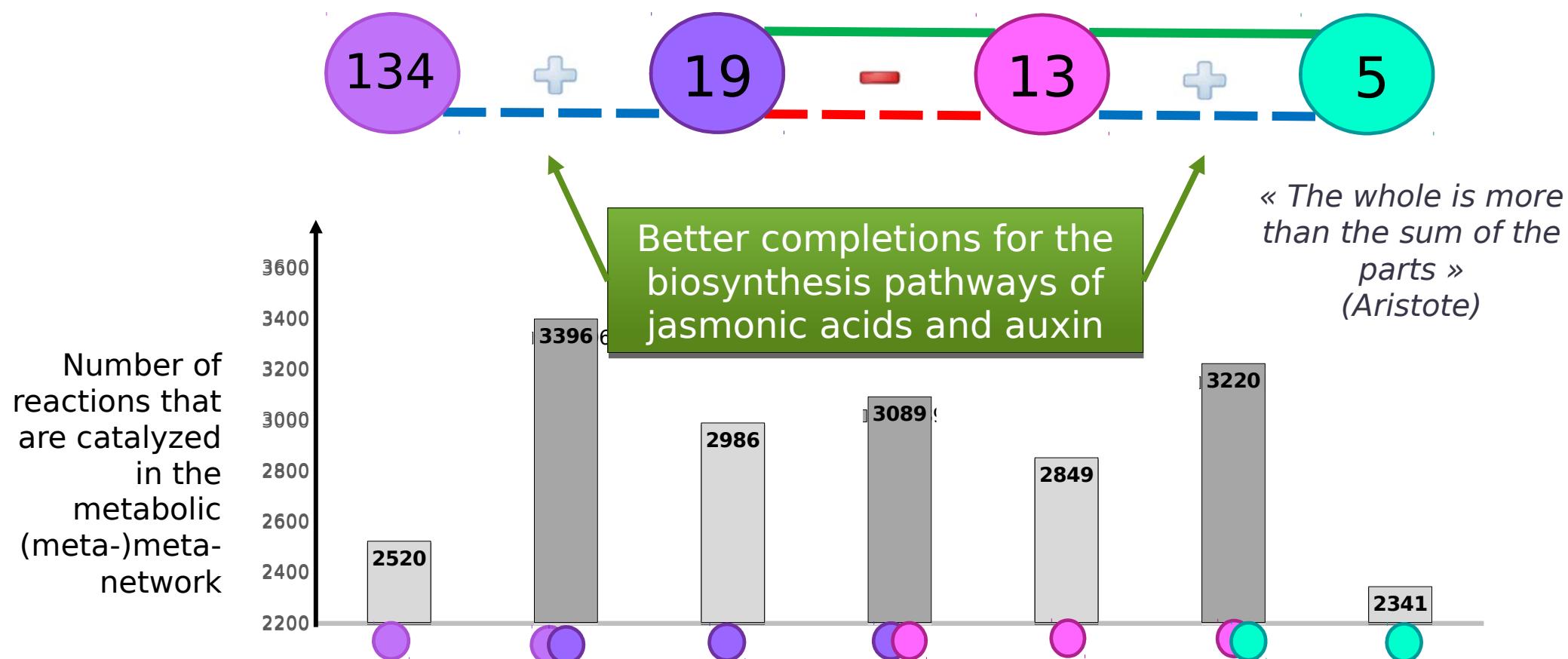
2010

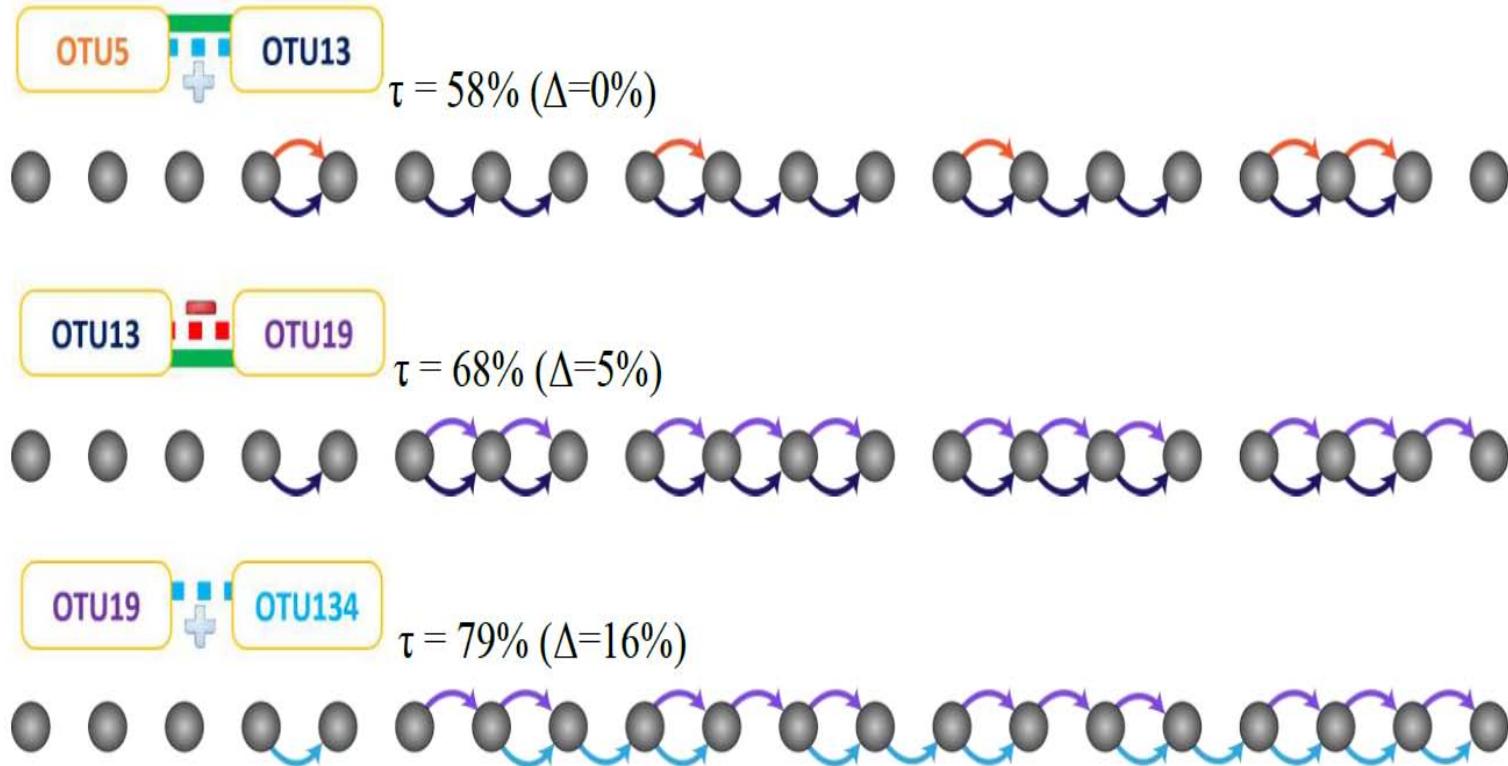


Evolution
in time



- SPIEC-EASI
- SparCC<0
- SparCC>0





Potdevin et al., 2017, en préparation

A