Reasoning over large-scale biological systems with heterogeneous and incomplete data

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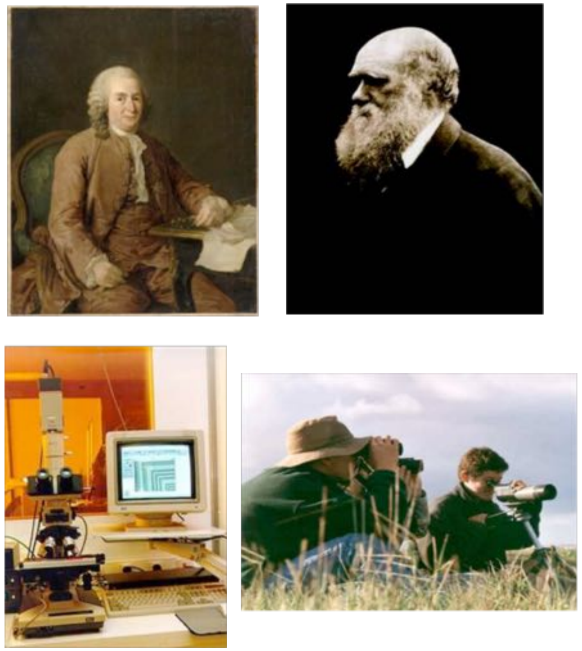
Dyliss team (Univ Rennes, Inria, CNRS)

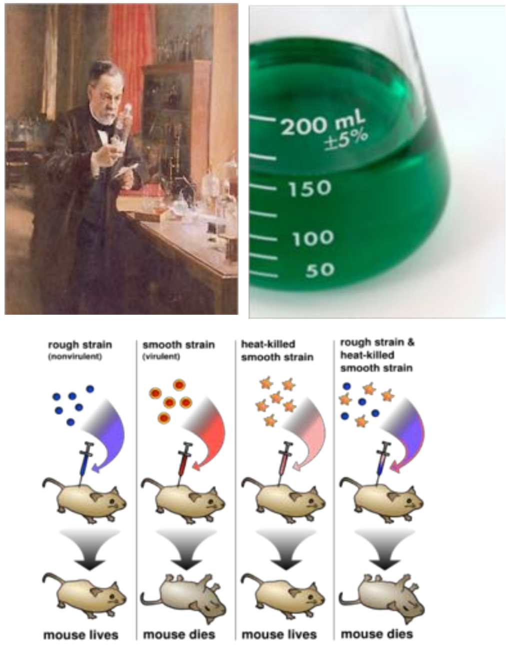
Short presentation

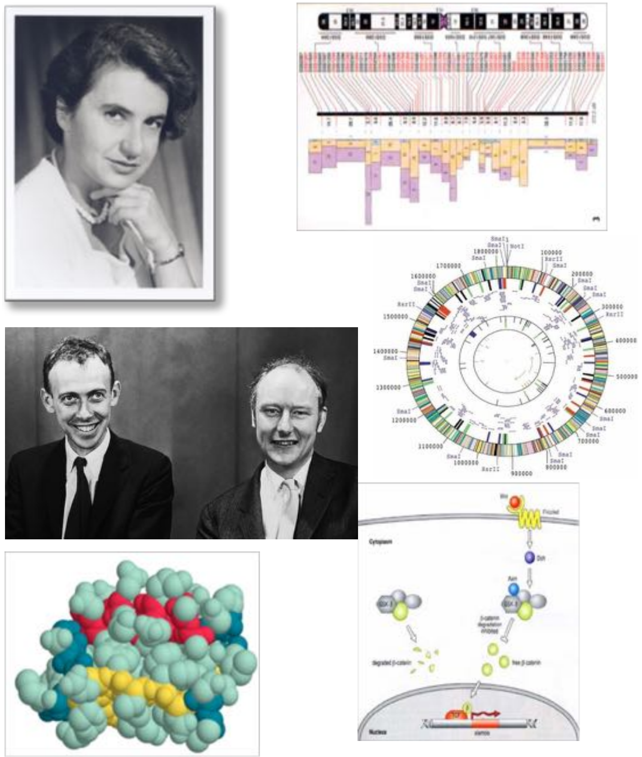
- **Reasearch field**
  - Discrete dynamical systems & fractals
  - Systems biology
  - Knowledge representation
- **IRISA & INRIA Rennes**
  - 800 members, >40 teams
  - Univ Rennes, CNRS, Inria, etc…
- **Bioinformatics@Rennes**
  - GenOuest: plateform, ressource center
  - Genscale : NGS data analysis
  - **Dyliss: Integration of heterogeneous data**

LIFE SCIENCE DATA

From life science… to data science




200 mL
±5%
150
100
50
rough strain (nonvirulent)
smooth strain (virulent)
heat-killed smooth strain
rough strain & heat-killed smooth strain
mouse lives
mouse dies
mouse lives
mouse dies



Naturalist approach

- Observing and deducing

Experimental approach

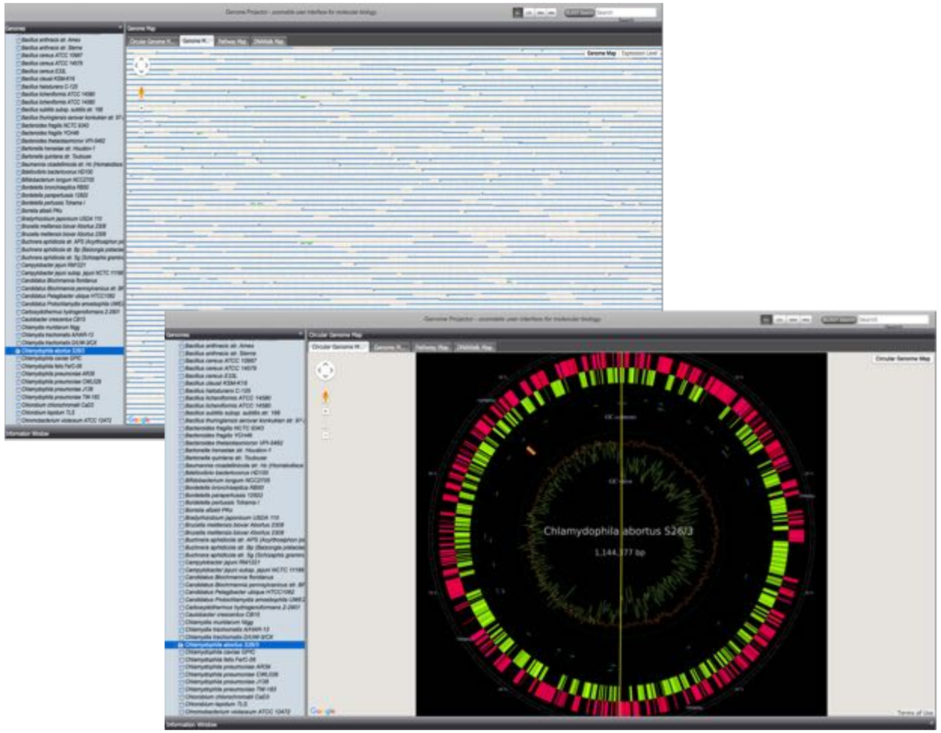
- Perturbating and observing

Modern biology

- Measuring at lower scales

→ **Data science !**

Biomolecular data: genomes



Genome sequencing

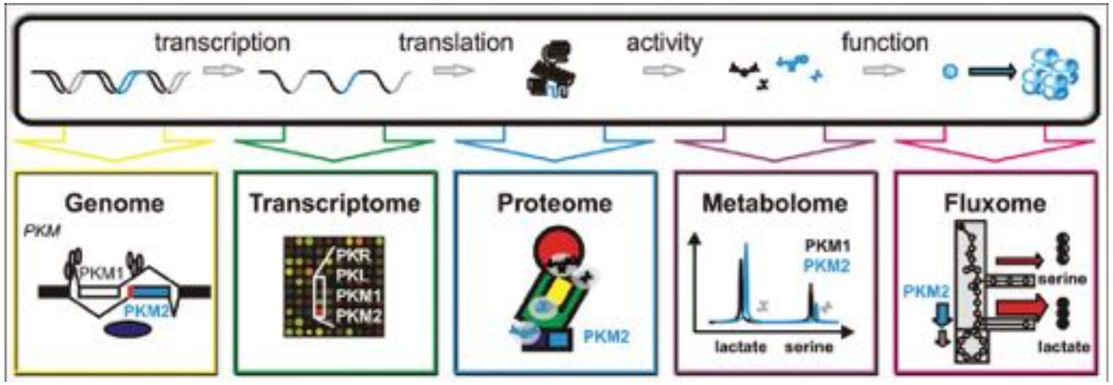
- Very smart computational issues
- Bioinformatics

Thousands of publicly available genomes

- Exploration, mapping and analysis

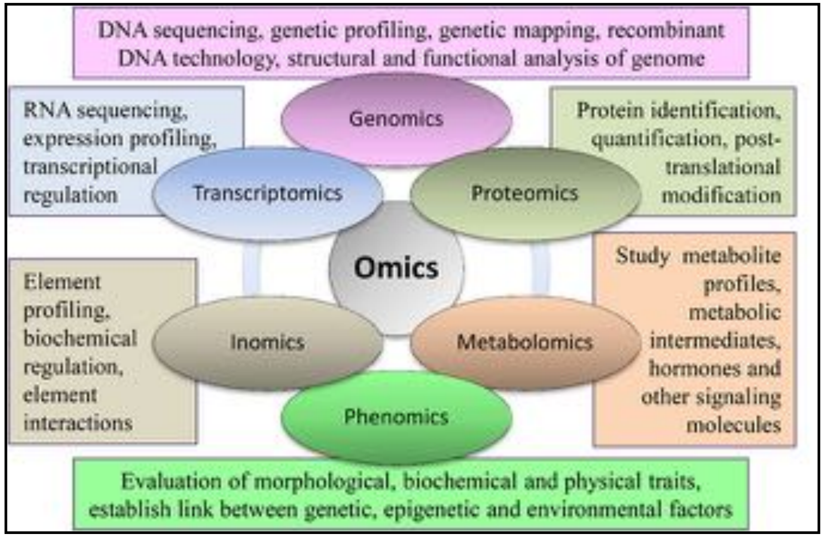
http://www.g-language.org/g3/

What do we do with genomic data ?



Assign a function to each DNA fragment

Develop new technologies to validate/refine the assigned functions



DNA sequencing, genetic profiling, genetic mapping, recombinant DNA technology, structural and functional analysis of genome

RNA sequencing, expression profiling, transcriptional regulation

Protein identification, quantification, post-translational modification

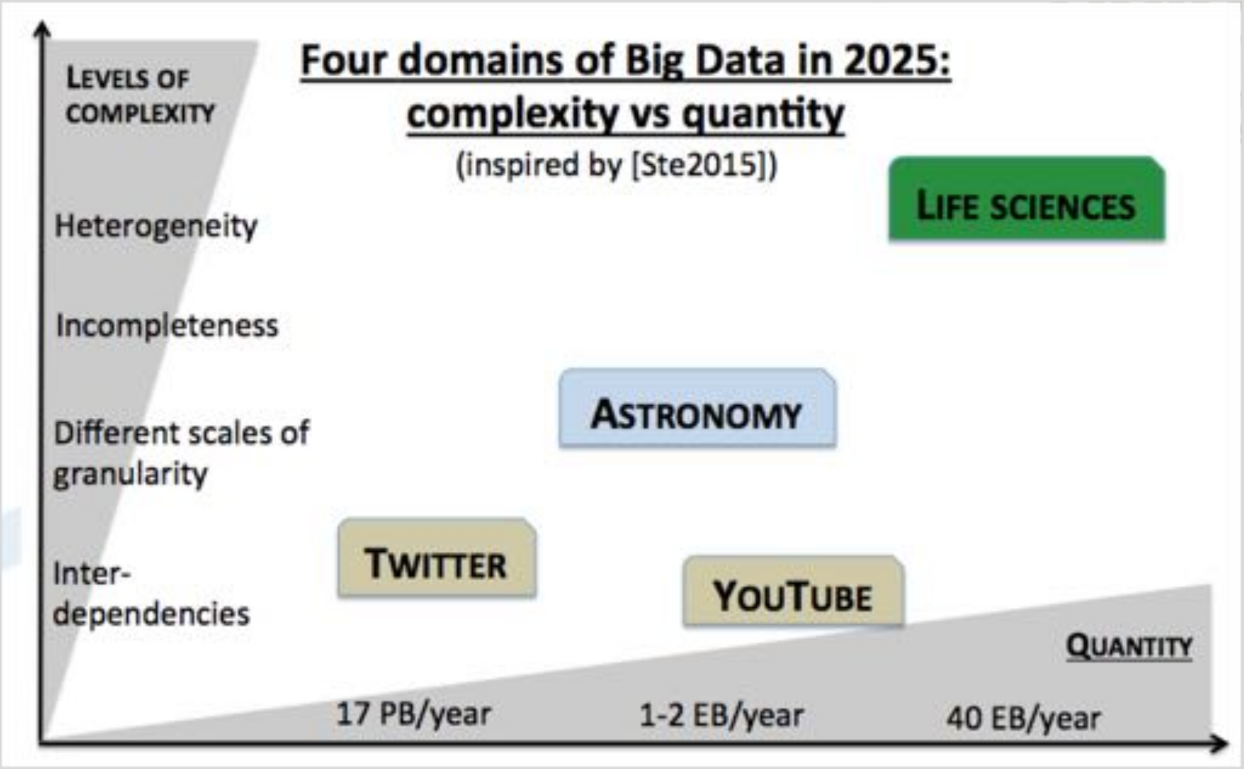
Element profiling, biochemical regulation, element interactions

Study metabolite profiles, metabolic intermediates, hormones and other signaling molecules

Evaluation of morphological, biochemical and physical traits, establish link between genetic, epigenetic and environmental factors

Data deluge !

Life science data nightmare



Four domains of Big Data in 2025: complexity vs quantity

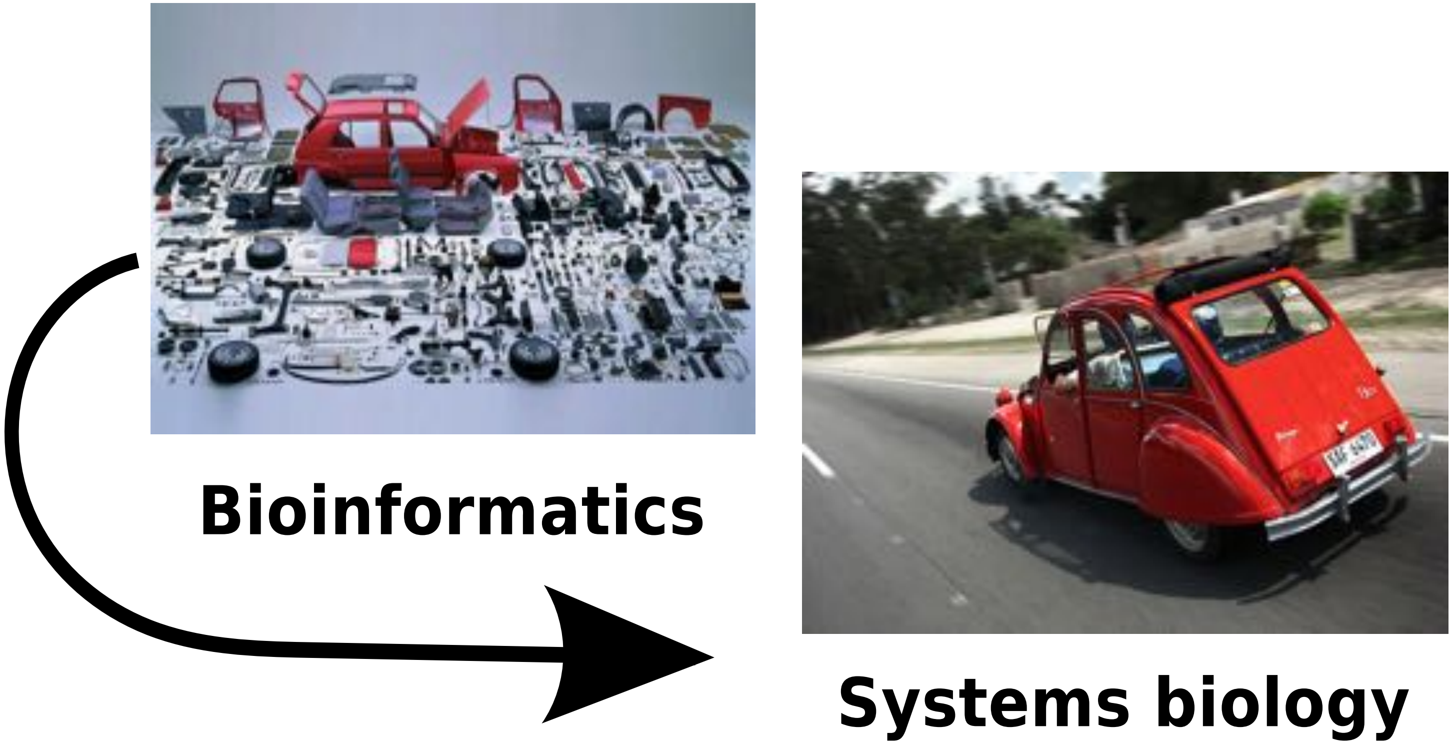
(inspired by [Ste2015])

Data characteristics

- Large-scale
- Incomplete
- Inter-dependent
- Heterogeneous / multi-scale

How to integrate them?

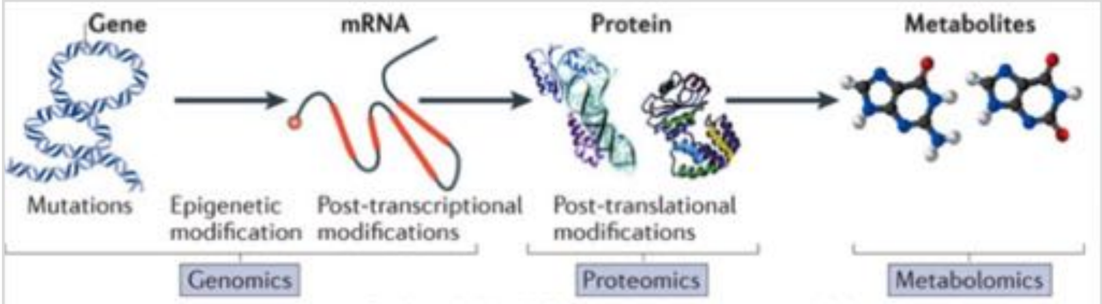
SYSTEMS BIOLOGY



Bioinformatics

Systems biology

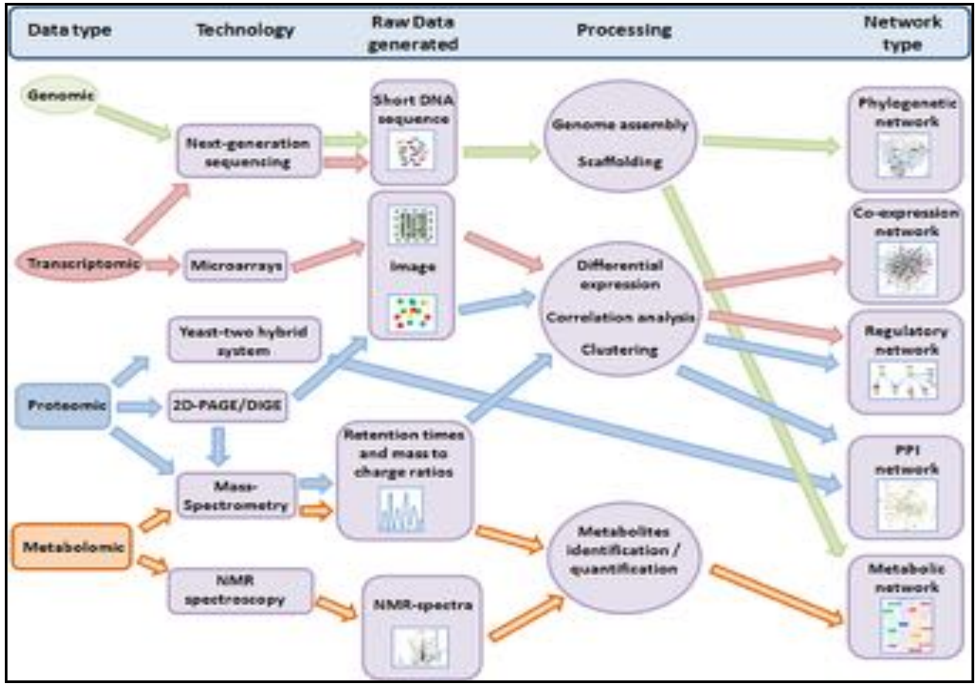
Setting all together



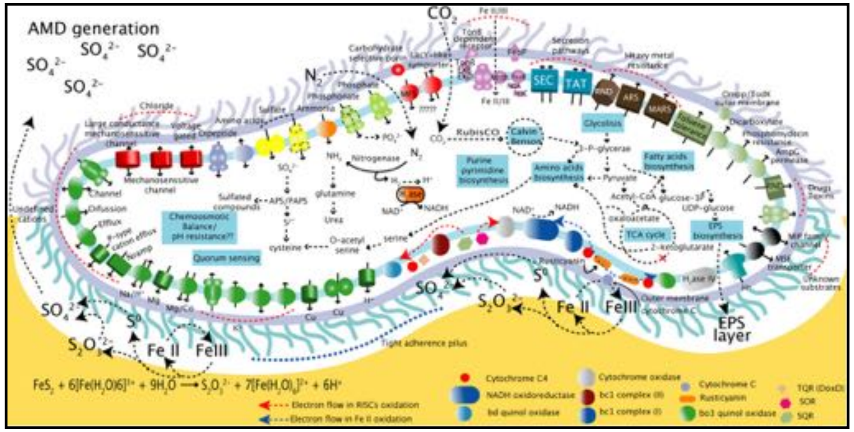
Patti et al. (2012). Metabolomics: the apogee of the omics trilogy. Nature

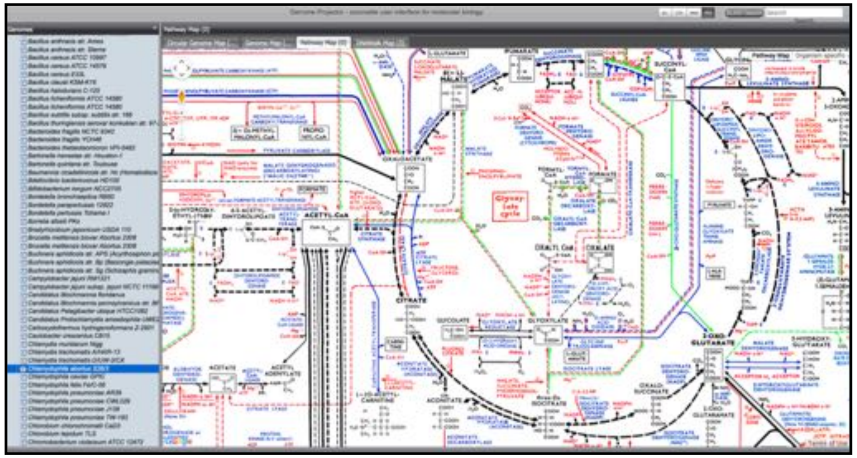
Gene function = regulation of a intra-cellular transformation procedure

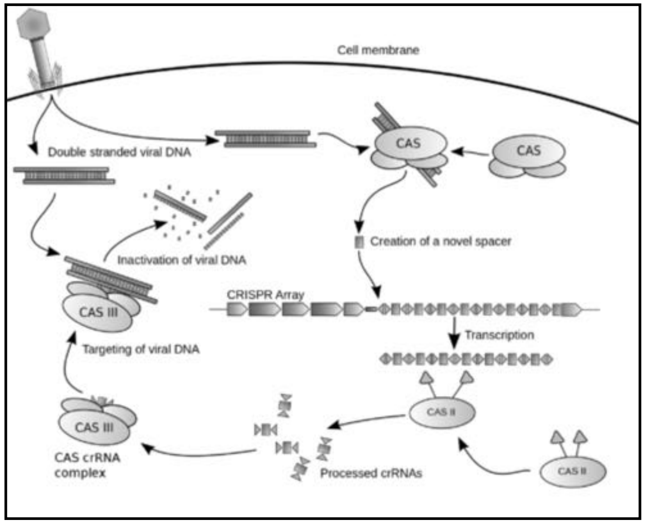
- Biological interactions !
- Graphs / networks

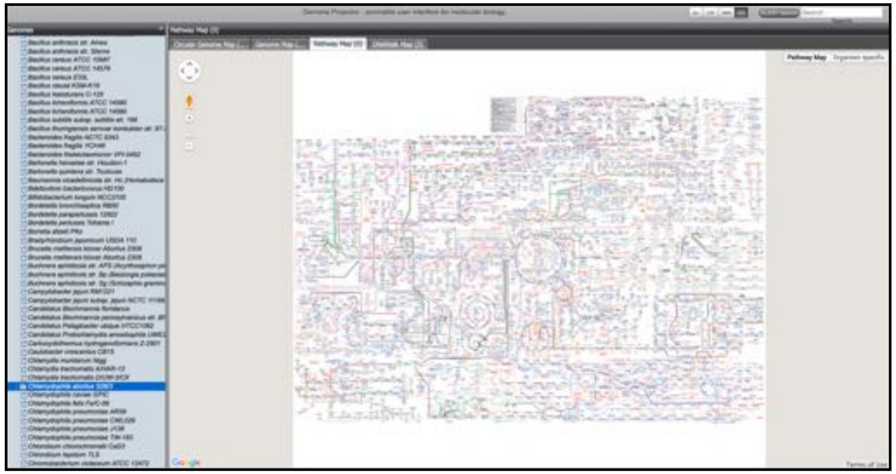


What we get…







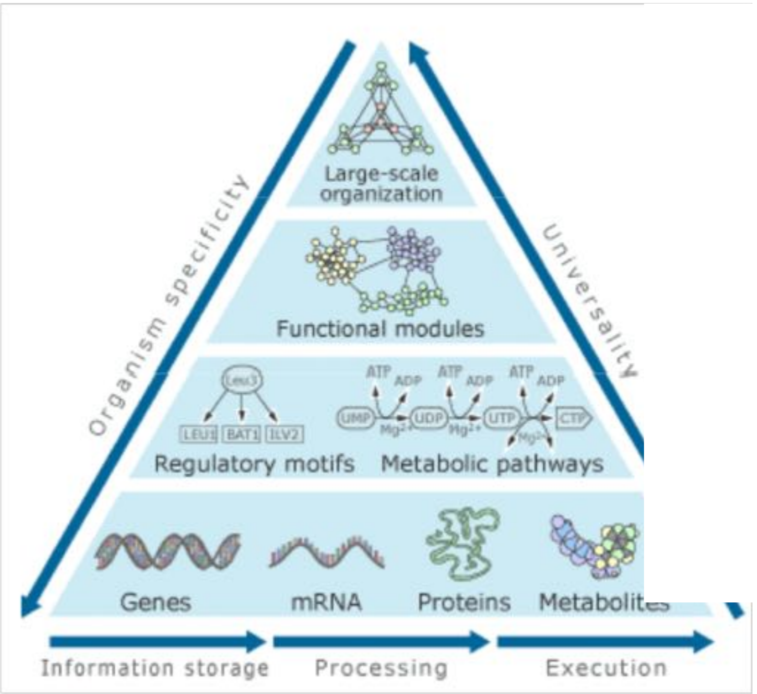


Large-scale graph description of interactions between compounds

Systems biology

Statement : biology is a complex system

- *« Requires to examine the structure and dynamics of a cellular function rather than the characteristics of isolated parts of a cell »* (Kitano, 2002)

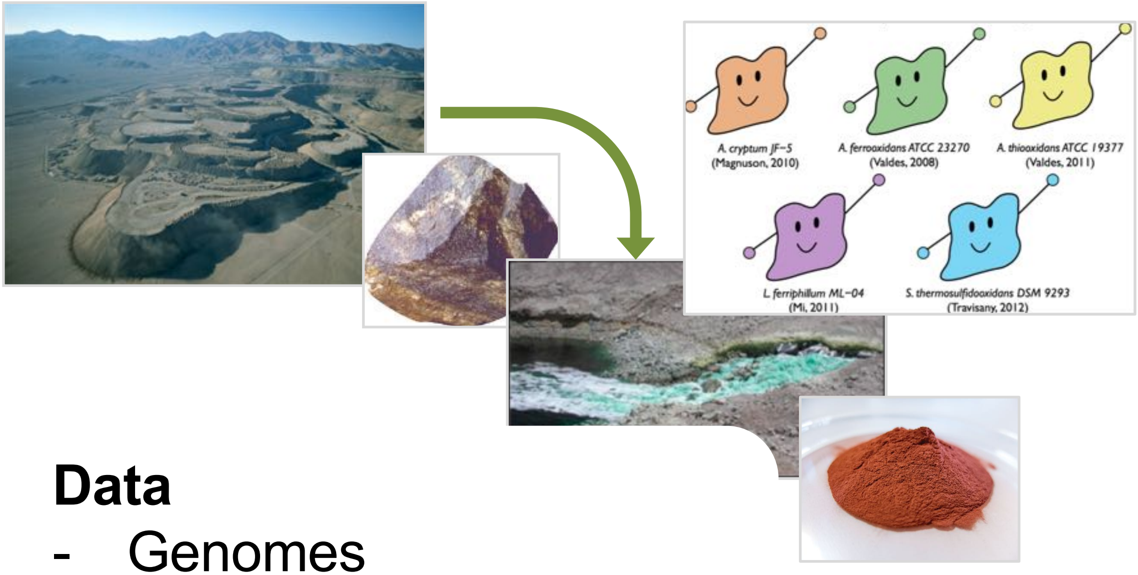


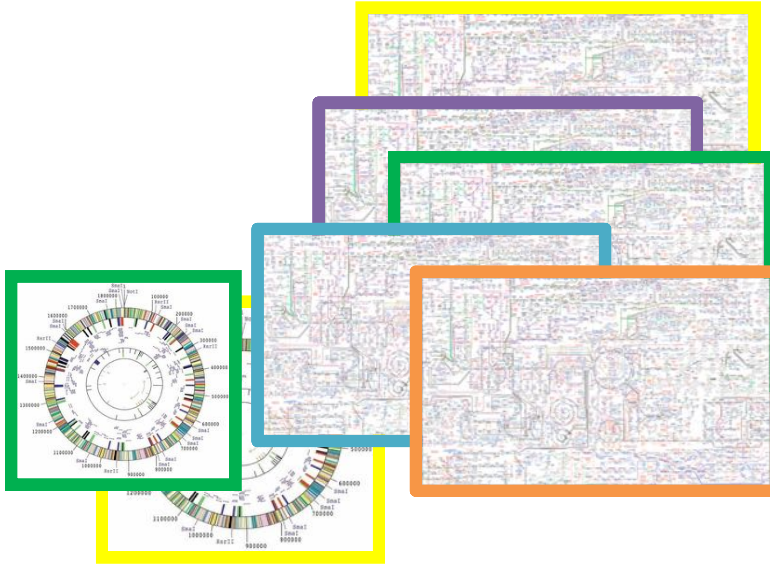
Systems biology: Interpreting multi-layer data and graphs

- Produce predictive statements that can be experimentally validated

Case-study: extremophile mining consortium

*Role of an **empirical taylor-made consortium** of bacteria in copper extraction from ore ?*





Data

- Genomes
- Expression data
- Metabolic compounds

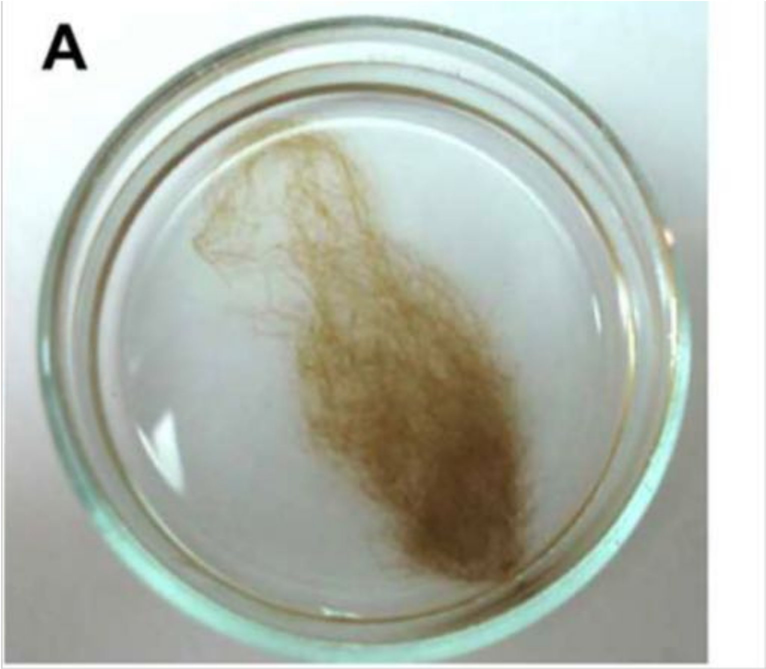
Turn data into

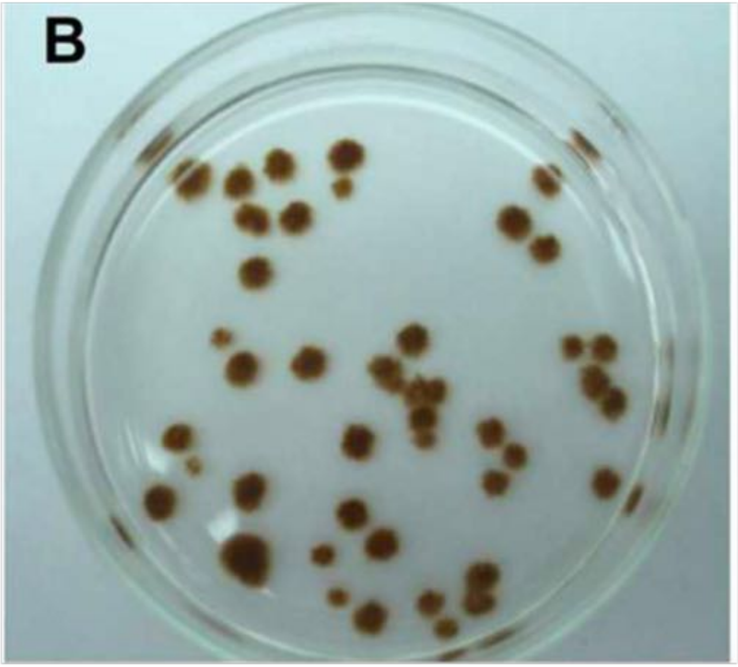
- genomics maps
- interaction maps

Understand the contribution of each bacteria to the complete system ?

➢ **integrative and systems biology**

A second case-study : algal metabolism





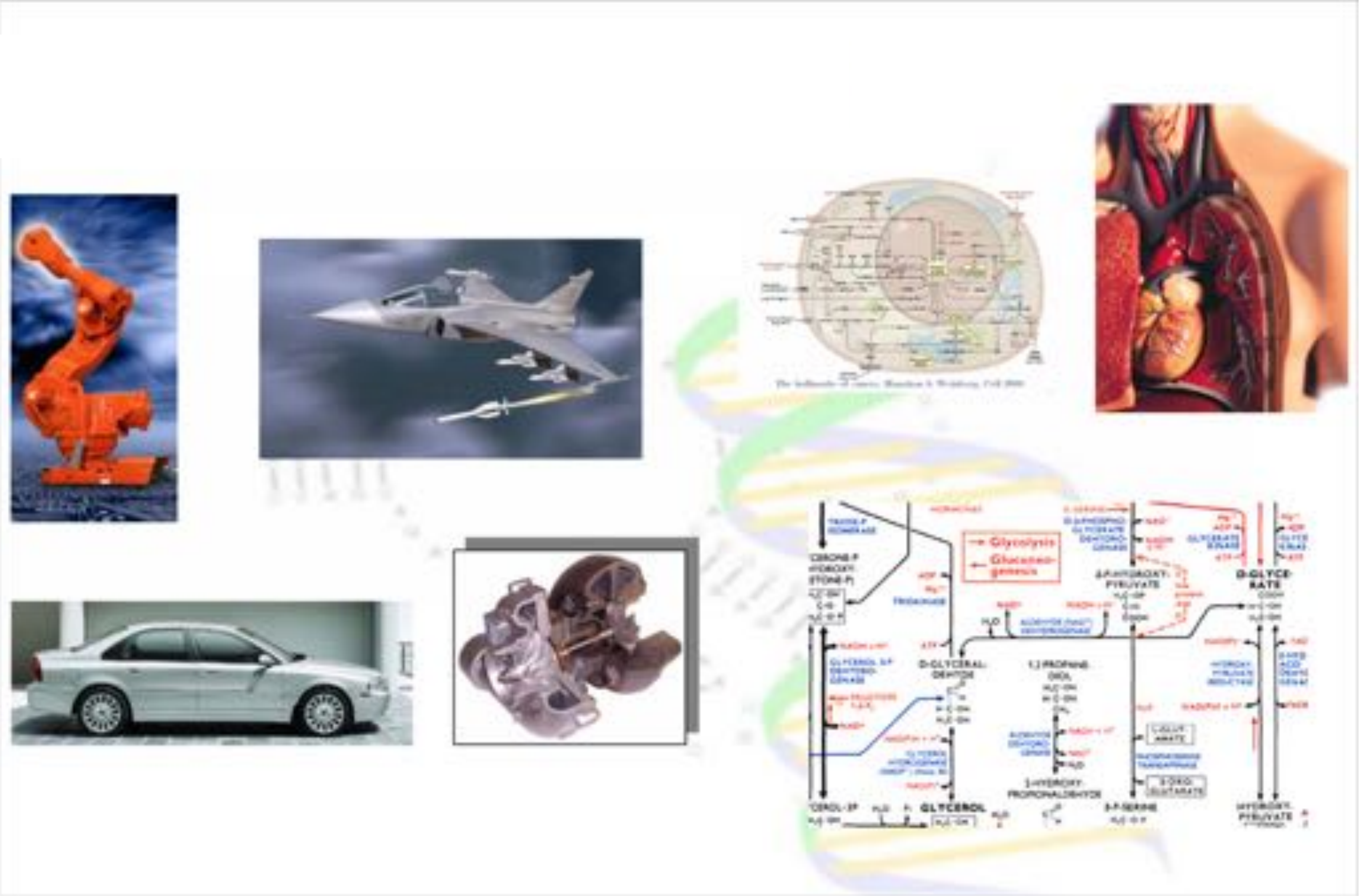
E. siliculosus

In axenic condition….

Ectocarpus
[Dittami2014, Tapia2016]

What is the role of environmental bacteria ?

Complex systems are everywhere



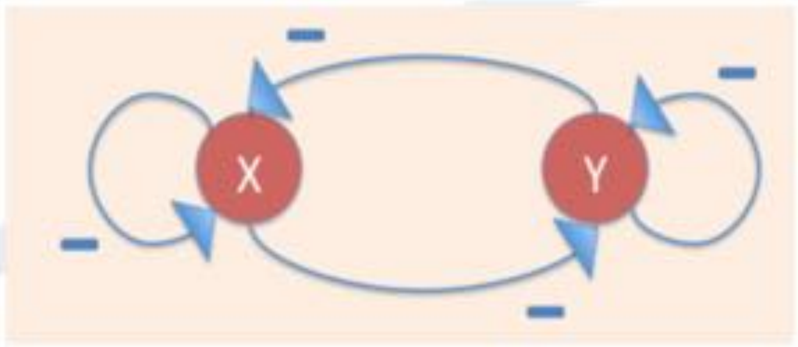
Are molecular/cellular different than others ?

Dynamical systems

Historical motivation

Model the evolution of the set of components in a system according to time.

$$\begin{array}{lcccccl} F: & \mathbb{T} & \times & \mathbb{S} & \to & \mathbb{S} \\ & (t & , & \mathbf{z}) & \mapsto & F(t,\mathbf{z}) \\ & (\text{time} & , & \text{state}) & & \text{new state at time } t \end{array}$$



$$\frac{dX}{dt} = \frac{k}{K+Y^n} - aX$$
$$\frac{dY}{dt} = \frac{l}{L+X^n} - bY$$

Parameterized numerical system

$$f(X) \leftarrow 1 - Y$$
$$f(Y) \leftarrow 1 - X$$

Boolean model with asynchronous update scheme

Identification/calibration of a dynamical system

Find the **best function F** which parcimounously explains and describes the observed responses of a system.

Model identification/calibration since the 18th century

What has always allowed a model identification

- **A priori knowledge about the (conservation/behavior) laws governing the system**
  - Predetermined shape for the function F
- **Limited number of components**
  - Reduction of the search space
- **Wide panel of sensors and perturbations**
  - Discriminate parameters

$$\begin{array}{lccccccc} F: & \mathbb{T} & \times & \mathbb{S} & & \to & \mathbb{S} & \\ & (t & , & \mathbf{z}) & & \mapsto & F(t,\mathbf{z}) & \\ & \text{(time} & , & \text{state)} & & & \text{new state at time } t & \end{array}$$

Where is the complexity ?

- The search space grows exponentially with the number of measured compounds

**The more compounds we measure,
the less calibrated a system can be.**

Differences between application domains

Physical sciences

- **Knowledge.**
  Fundamental laws of physics.
- **Sensors.**
  Numerous.
- **Perturbations.**
  Various protocoles in controled frameworks.
- **System description.**
  Independent components

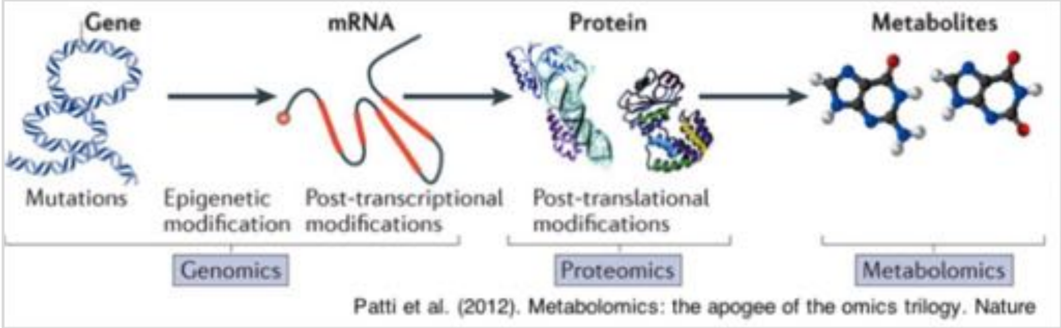
Biological sciences

- **Knowledge.**
  Empirical laws
- **Sensors.**
  Low quality (qualitative) although numerous.
- **Perturbations.**
  Quite few according to sensors
- **System description.**
  Hidden dependencies

Today's molecular/cellular biological systems

Omics data.

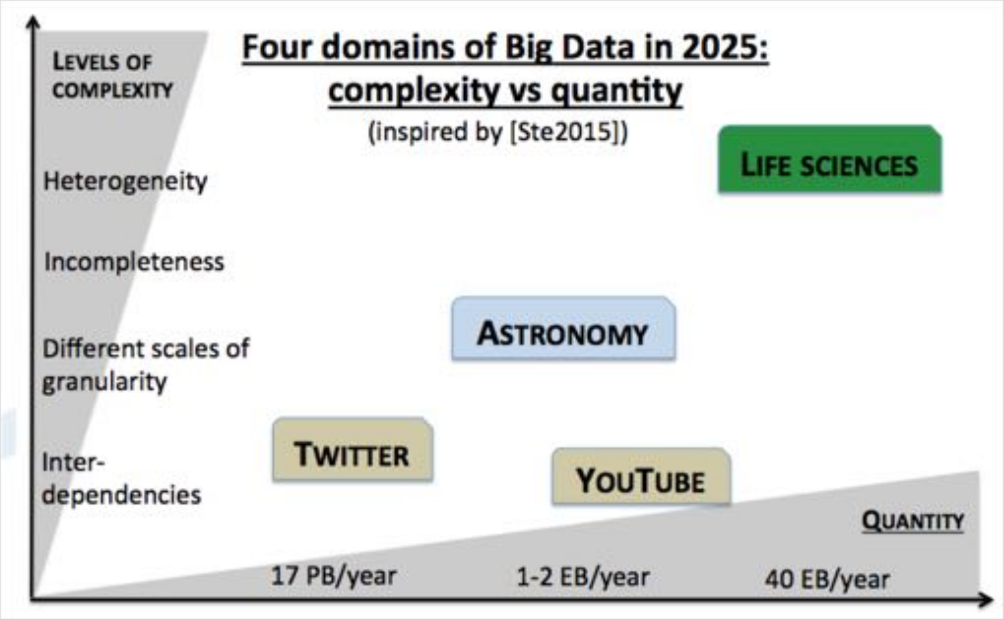
- ➢ Large-scale (variables)
- ➢ Noisy
- ➢ Heterogeneous.



Patti et al. (2012). Metabolomics: the apogee of the omics trilogy. Nature

Biological systems characteristics

- ➢ Large-scale
- ➢ Empirical laws
- ➢ Few data wrt the search space size



Biological systems observed with omics data cannot be uniquely determined

Strategy: combine dynamical systems and constraints programming

Describe a system by a family of abstract models

- Reason over a family of models instead of selecting a single one

(Logical) knowledge representation

- Search space **description**
- Structured knowledge (link open data)

Discrete dynamical systems

- **Links** between multi-scale observations.
- **Invariants** of model families.

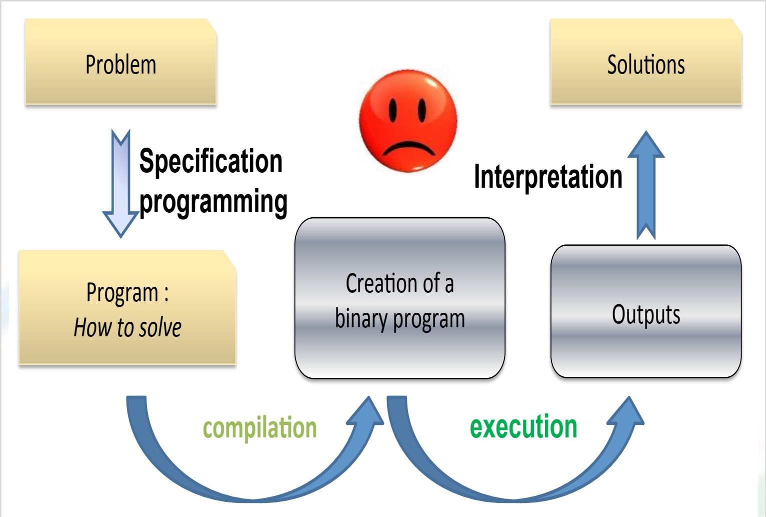
Solving optimisation problems

- **Replace laws by constraints**
- Extract robust information

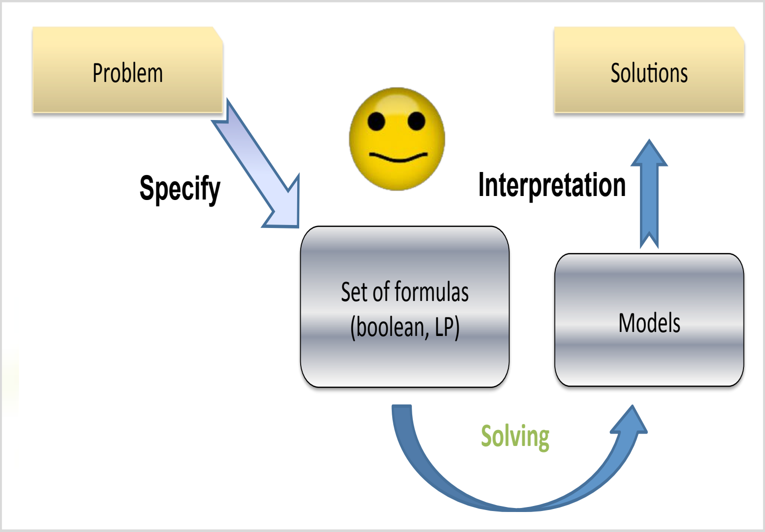
KNOWLEDGE REPRESENTATION

```
1{murderer(ms_Scarlet); murderer(colonel_Mustard)}1.
1{weapon_of_crime(revolver); weapon_of_crime(candlestick)}1.
1{place_of_crime(kitchen); place_of_crime(hall);
                              place_of_crime(dining_room)}1.

crim_record(ms_Scarlet,7). crim_record(colonel_Mustard,4).

weapon_of_crime(candlestick).
:- place_of_crime(kitchen).
place_of_crime(hall) :- murderer(colonel_Mustard), not
                                     weapon_of_crime(revolver).

sol(X,Y,Z) :- murderer(X),weapon_of_crime(Y),place_of_crime(Z).
#maximize{W , sol : sol(X,Y,Z) , crim_record(X,W) , murdered(W)}.
#show sol/3.
```

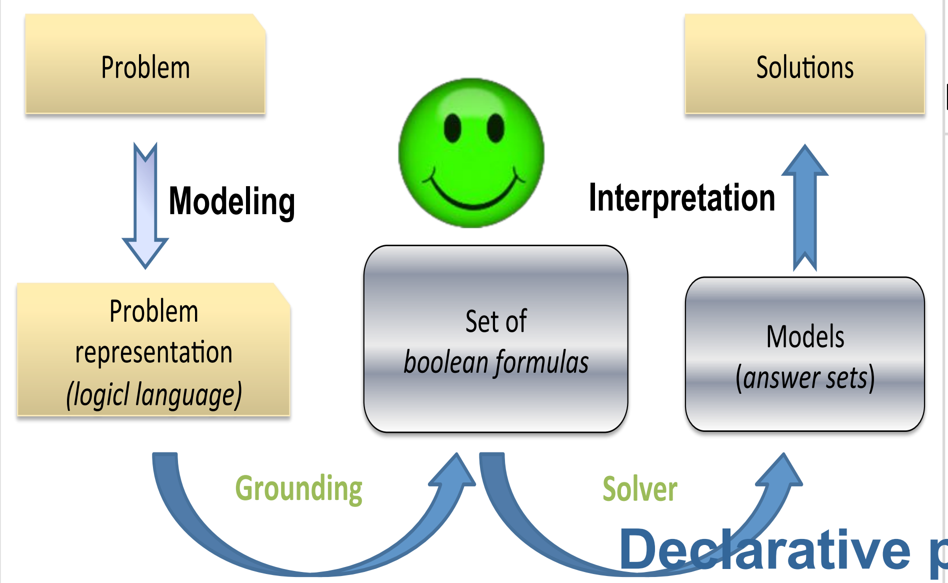
Solving combinatorial problems



Write a program whic
how the problem sho



ite (boolean, linear)
nstraints (*SAT, ILP,…)*



Answer set programming.
Describe what you want to solve

Declarative programing

- **Problem = axioms & rules**
- **No need of algorithm**

ASP logical rules : declarative programming

$$\underbrace{K\ \{\ atom_1;\ \ldots;\ atom_n\ \}\ L}_{\text{head}}\ \underbrace{\text{:-}}_{\text{"smiley"}}\ \underbrace{atom_{n+1}\ ;\ldots;\ atom_r;\ \ not\ atom_{r+1};\ \ \ldots;\ \ not\ atom_s\ .}_{\text{body}}$$

If **all terms** on the **right side** are true,
then **at least K and at most L** terms are true on the **left side**.

If **nothing** on the **left side**,
then **always false.**

```
:- K{atom1, .. atomN}L.
```

If **nothing** on the **right side**,
then **always true.**

```
K{atom1, .. atomN}L.
```

Optimisation rule

```
#maximize{W,atom(X): condition(X),W}.
```

High-level model language

- ➢ Propositional logics
- ➢ Model for negation

Highly performant solving technics

- ➢ SAT-based and deductive-DB technics
- ➢ Decidable: no infinite loop

Link with systems biology ?

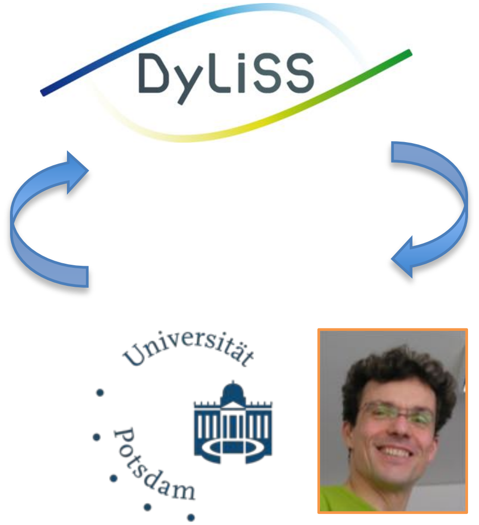
Integrative and systems biology is a very relevant field to challenge ASP technologies

- Repair large-scale interaction graph with **branch and bound** solving heuristics (KR 2010)
- Scale metabolic network completion problem with **unsatisfiable core** solving strategy (LPNMR 2013)
- Design experiments with **incremental solving** (Frontiers 2015)
- Implement and benchmark **constrains propagators** (TPLP 2018)

Linear constrains atoms

```
&sum{a1*x1;...;al*xl} <= k
```

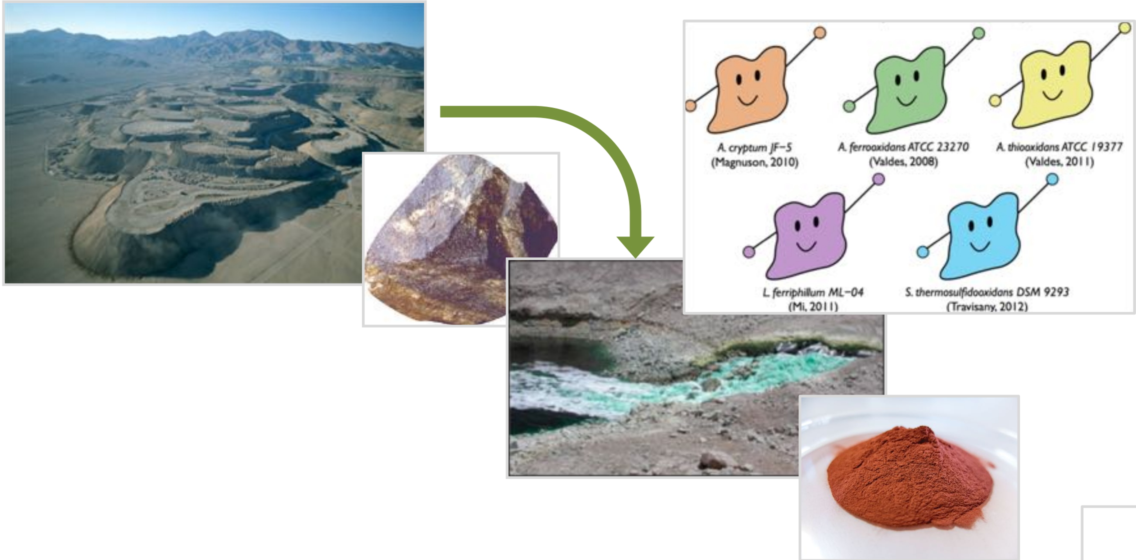
Problem statement
& modelling

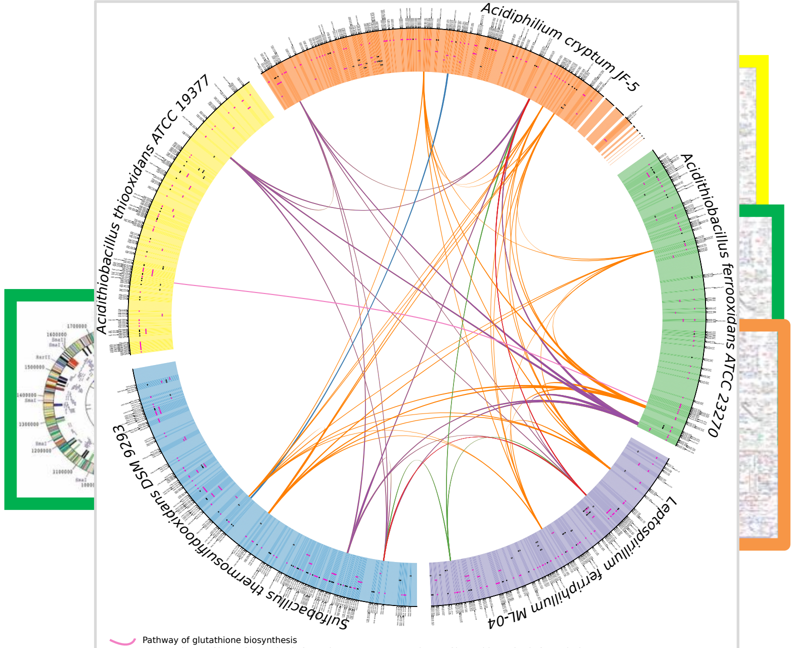


Solving heuristics
& problem reformulation

Application: extremophile mining consortium

*Role of an **empirical taylor-made consortium** of bacteria in copper extraction from ore ?*




Acidiphilium cryptum JF-5
Acidithiobacillus ferrooxidans ATCC 23270
Leptospirillum ferriphilum ML-04
Sulfobacillus thermosulfidooxidans DSM 9293
Acidithiobacillus thiooxidans ATCC 19377
Pathway of glutathione biosynthesis

*« **NAD(H) biosynthesis** metabolic pathways of **A. Cryptum** complements metabolic functions spread between the five strains »*

ASP program

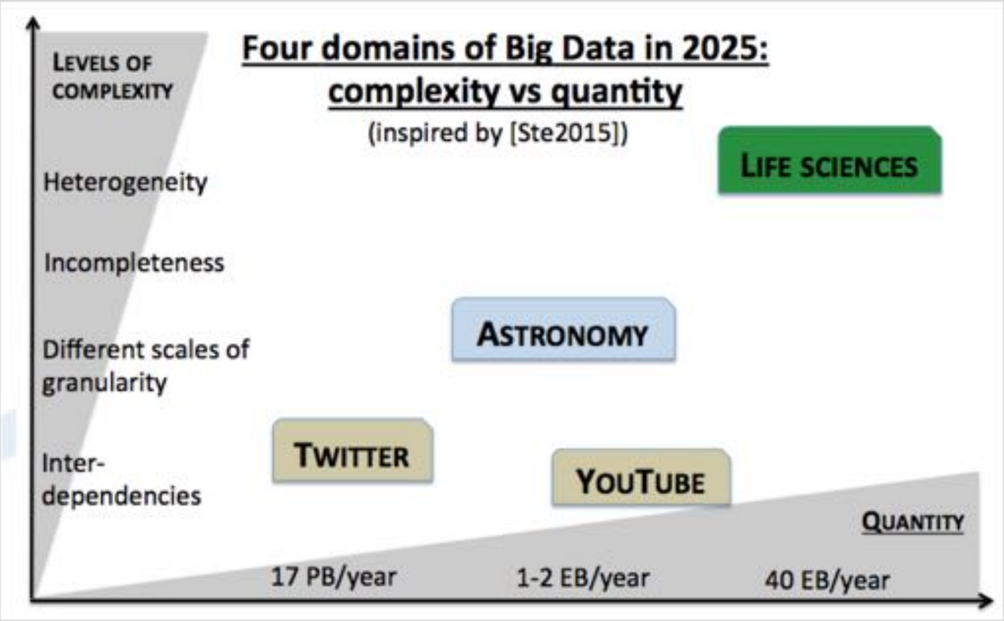
→ graph alignment / static modeling

→ chains of reactions explaining the capability of the consortium to produce the compounds (LPNRM'13, Microbiology open'15)

BACK TO DYNAMICAL SYSTEMS

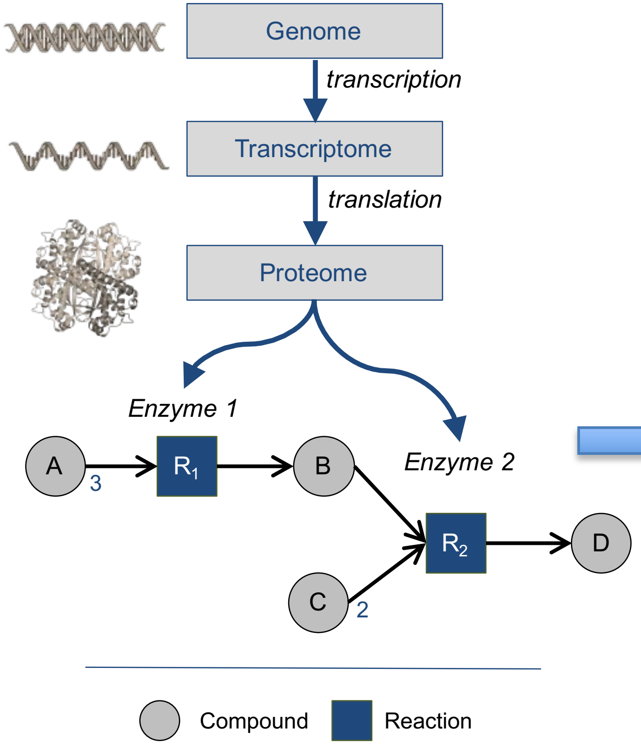
Biological systems characteristics

- ➢ Large-scale
- ➢ Empirical laws
- ➢ Few data wrt the search space size



Biological systems observed with omics data are not uniquely identifiable

Underlying tool : from genes to dynamical systems

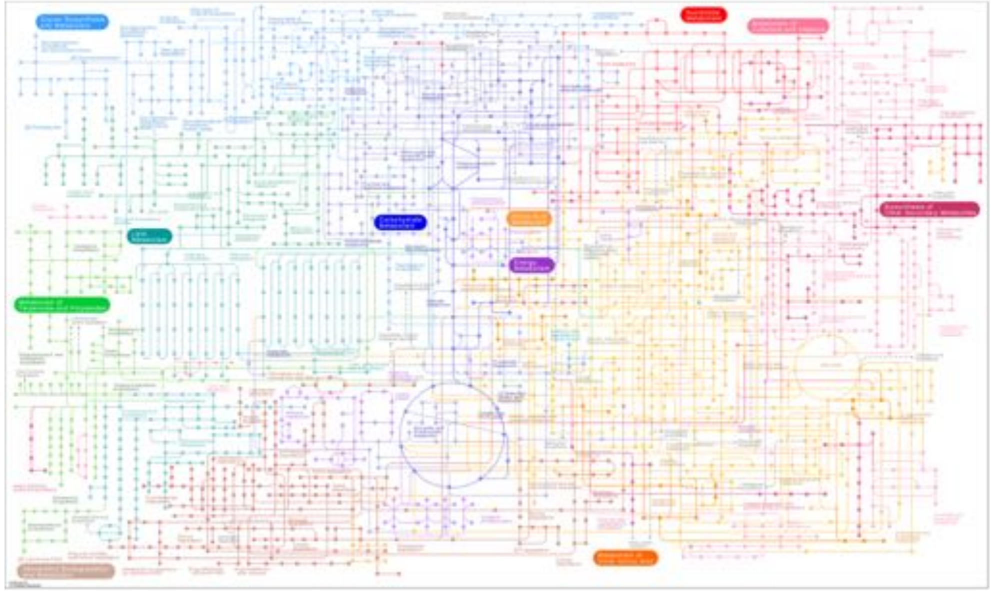


Link between genes and functions

1 genome

⇒ 1 metabolic network

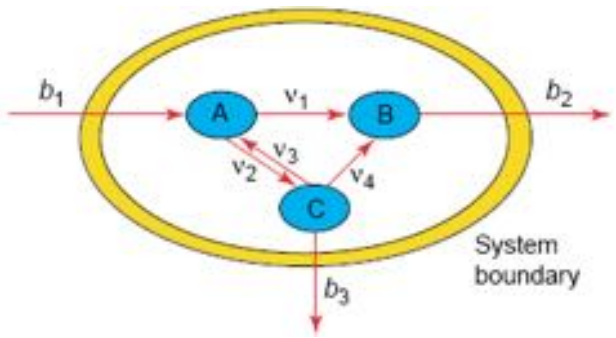
= bipartite directed graph



Large scale metabolic network

All expected metabolic capabilities of an organism

How to model fluxes ?



$$\frac{dA}{dt} = -v_1 - v_2 + v_3 + b_1$$

$$\frac{dB}{dt} = v_1 + v_4 - b_2$$

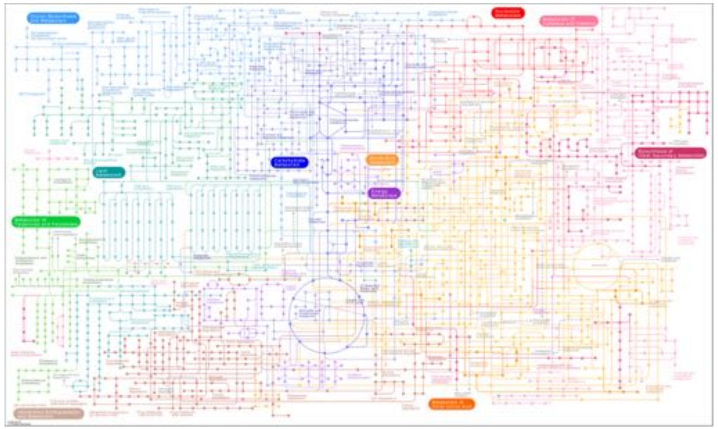
$$\frac{dC}{dt} = v_2 - v_3 - v_4 - b_3$$

$$\frac{dx}{dt} = S \cdot v(x)$$

$$v([substrat]) = Vm[Substrat]/(Km + [Substrat])$$

Back to high school chemistry

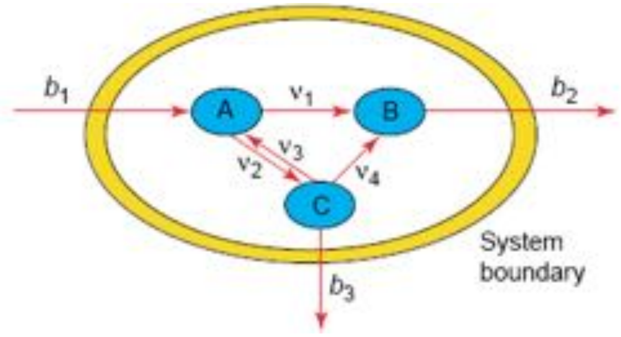
- ➢ Two parameters have to be estimated for each reaction



Intractable in practice !

- ➢ Overapproximation of the dynamics

Quasi-steady state hypothesis



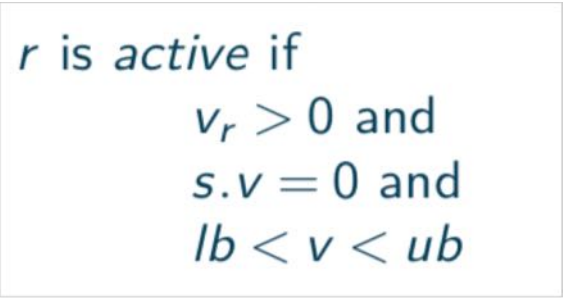
$$\frac{dx}{dt} = S \cdot v(x) = 0 = S \cdot v$$

$$v([substrat]) = Vm[Substrat]/(Km + [Substrat])$$

= *constant*

Metabolic compounds do not accumulate

- Fluxes have constant values
- Fluxes are constrained by linear values
- The system optimises a global objective



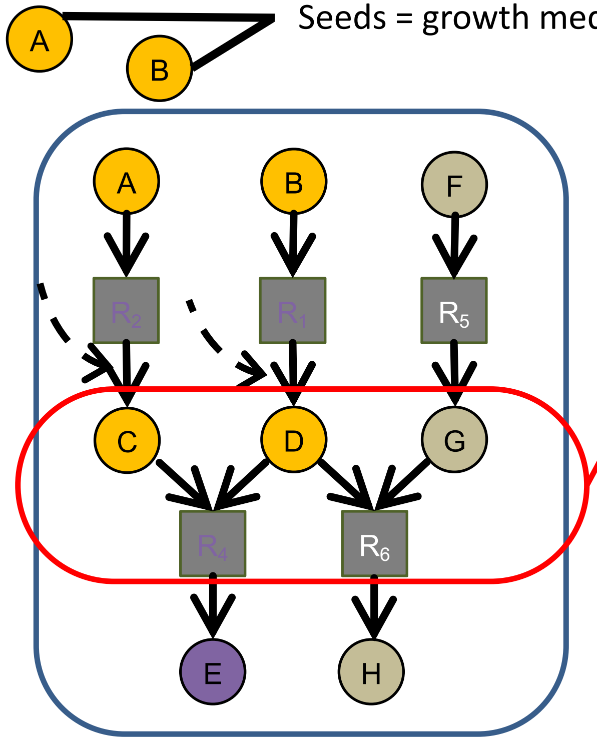
r *is active if*

$v_r > 0$ and
$s.v = 0$ and
$lb < v < ub$

Replace kinetic constants by conservation law and global optimisation hypotheses

Growing phase hypothesis

Functionality: recursive graph-based semantics



Seeds = growth medium

“and” condition checked recursively

F *Non-producible metabolite*

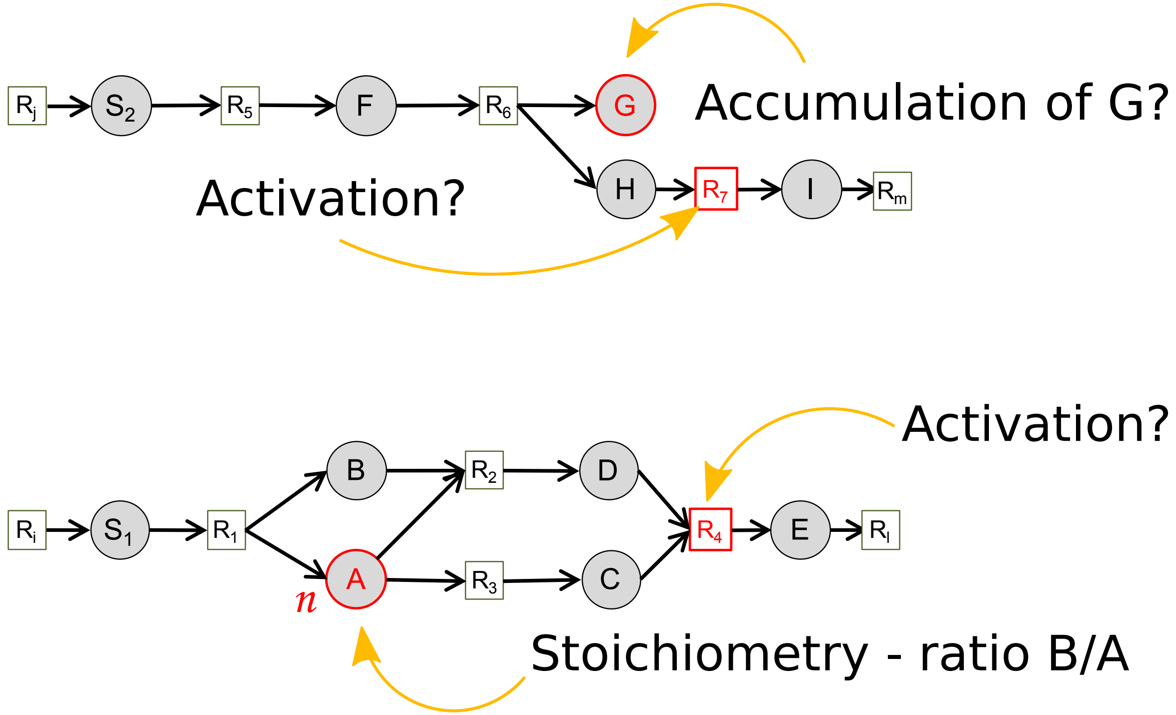
A *Metabolite reachable from the seeds*

R *Reaction*

```
scope(M):- seed(M).
scope(M):- product(M,R), reaction(R),  scope(M′) : reactant(M′,R).
```

Study paths in hypergraphs

Everything is a matter of choices



Accumulation of G?

Activation?

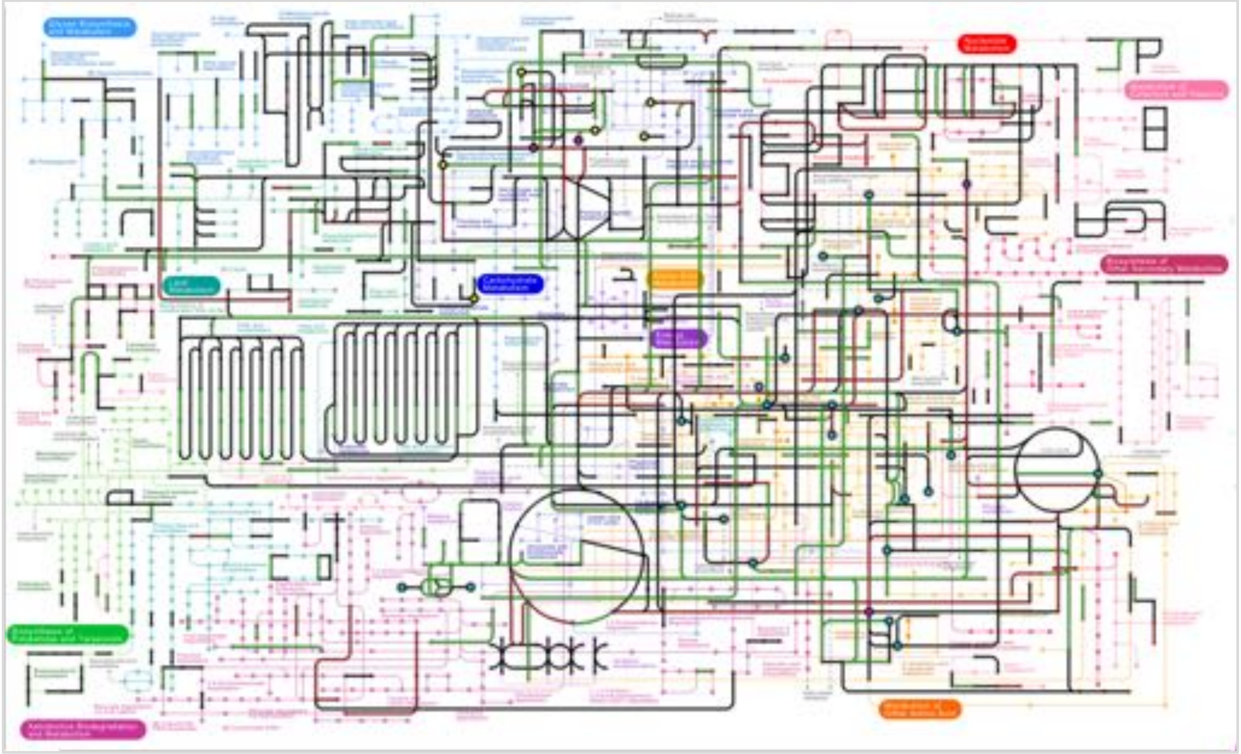
Activation?

Stoichiometry - ratio B/A

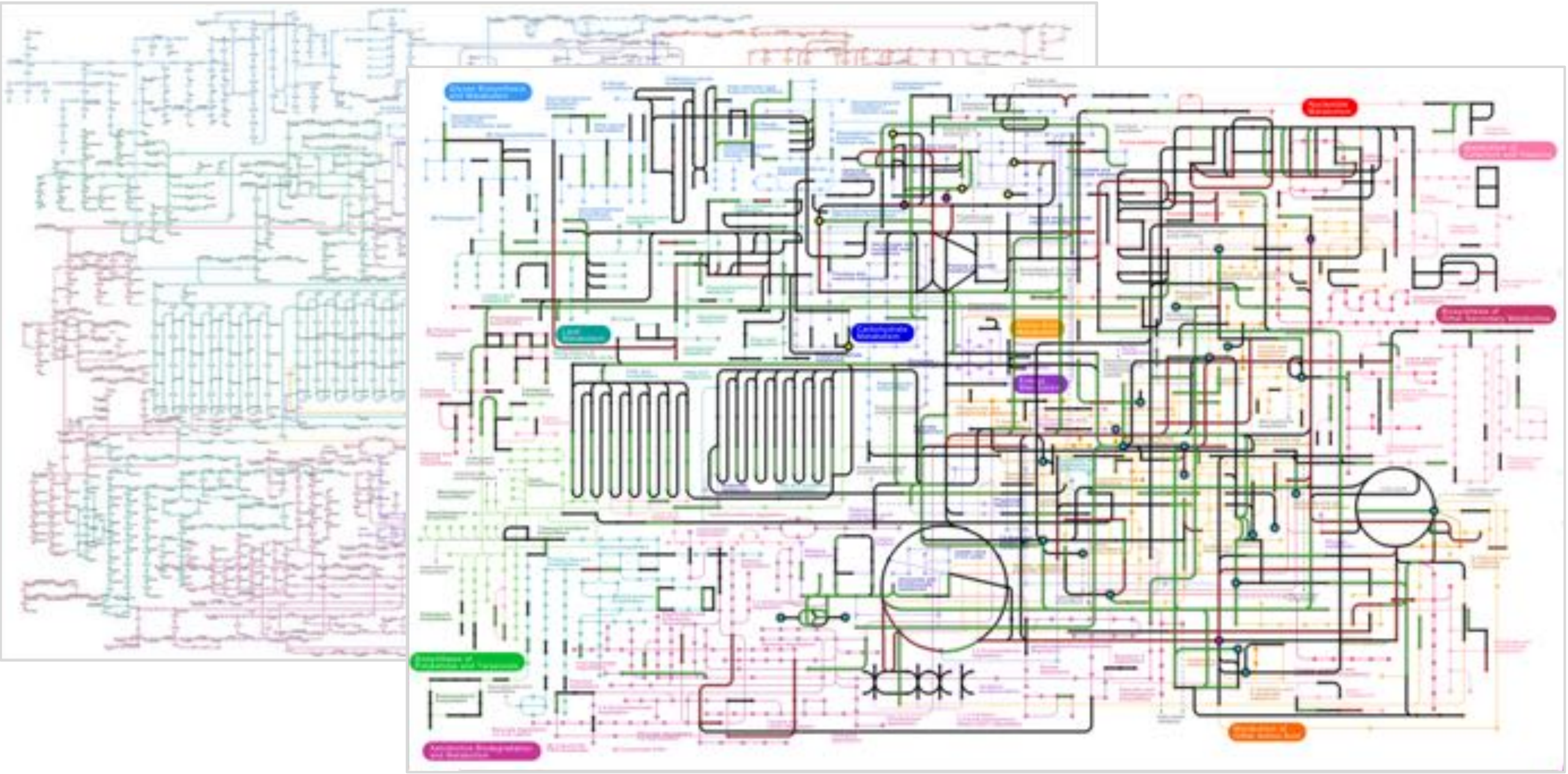
The reaction status of the reactions is different according to the approximation

- No choice but dealing with such overapproximation !
- Use the flexibility of ASP language to handle these questions

APPLICATION TO NETWORK COMPLETION


Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Lipid Metabolism
Carbohydrate Metabolism
Biosynthesis of Other Secondary Metabolites
Biosynthesis of Polyketides and Terpenoids
Xenobiotics Biodegradation and Metabolism
Metabolism of Other Amino Acids

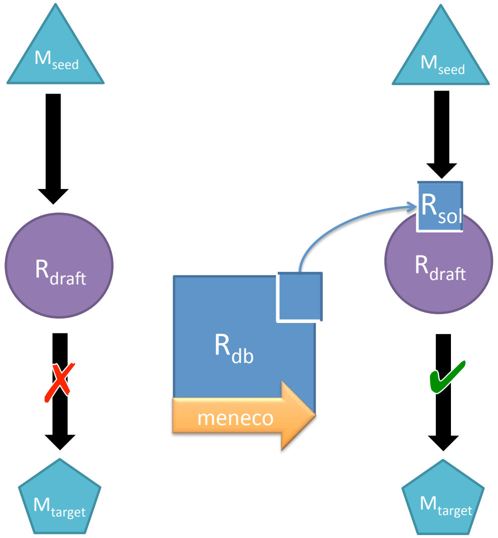
Data incompleteness



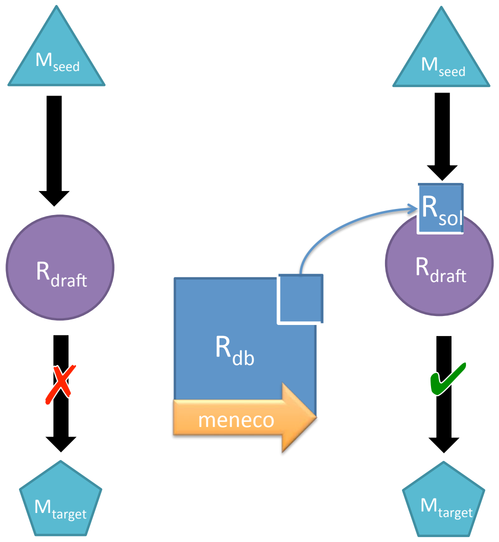
Metabolic networks built from NGS sequencing

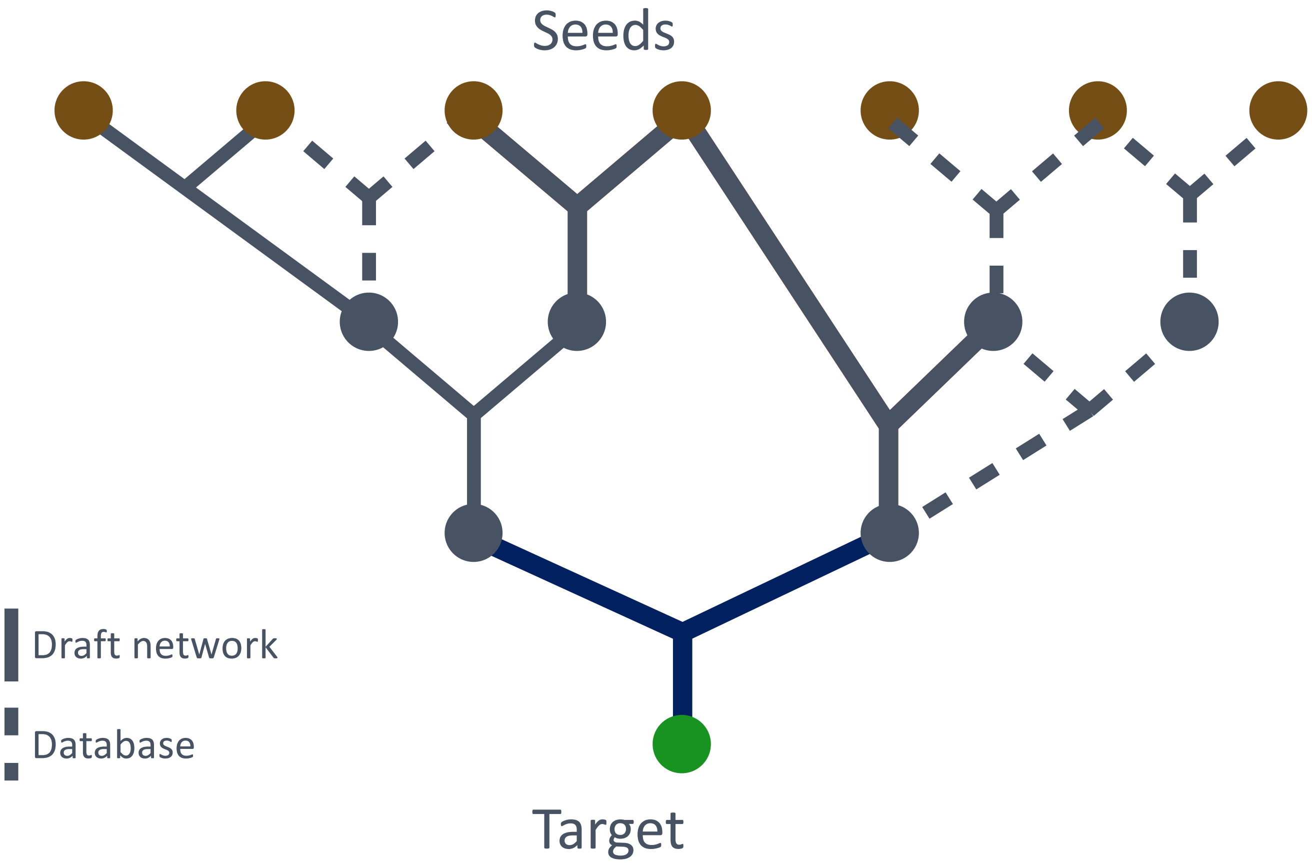
- ➢ no possible biomass production.

Gapfilling a metabolic network (nutshell)

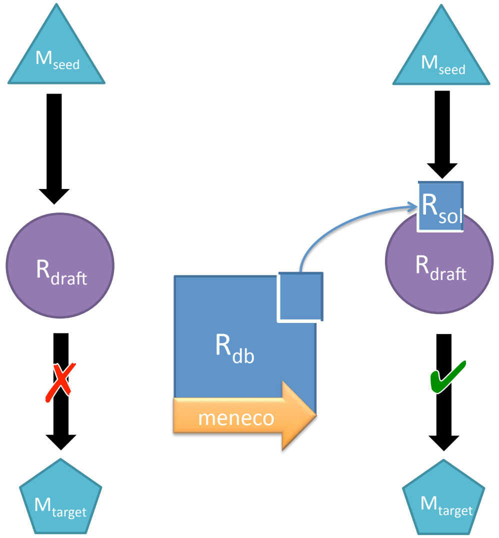


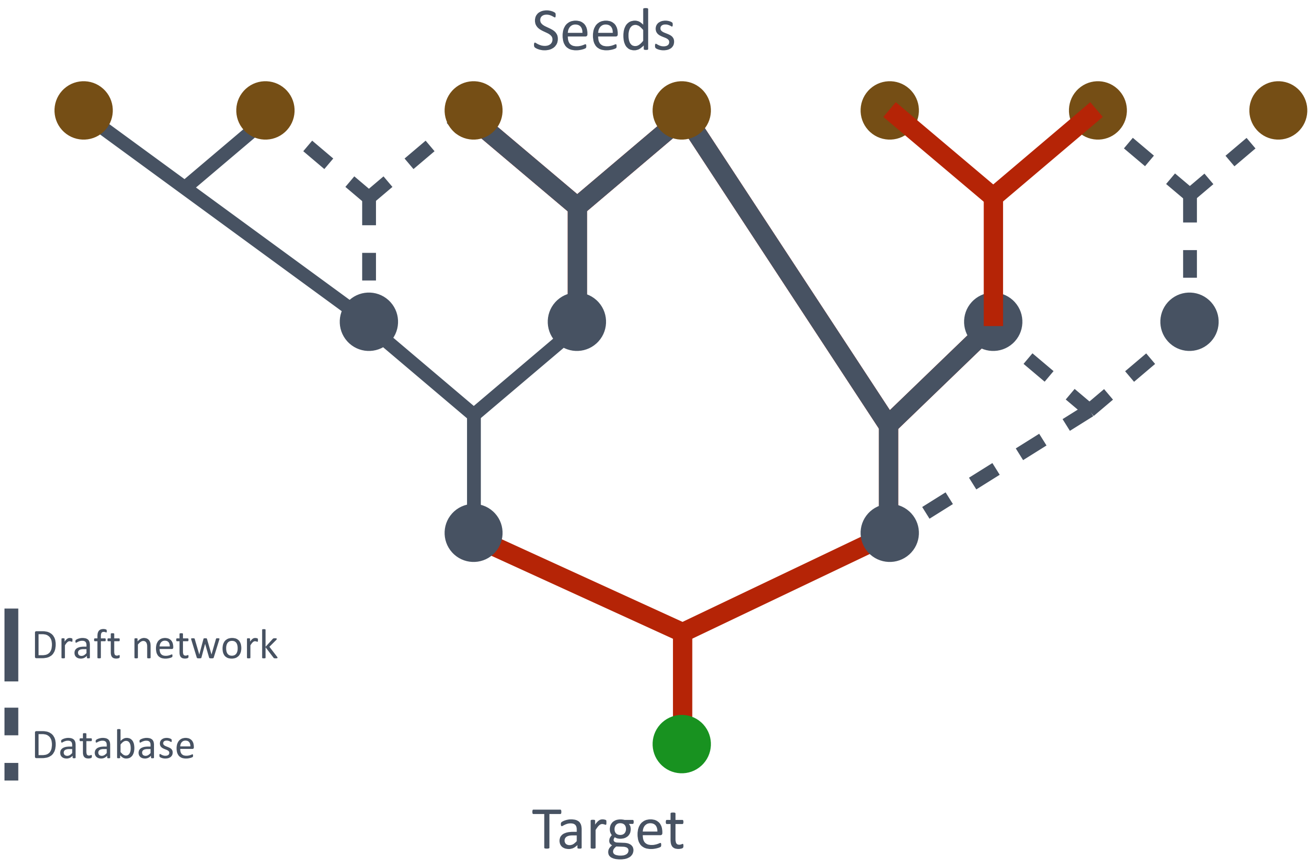
Gapfilling a metabolic network (nutshell)



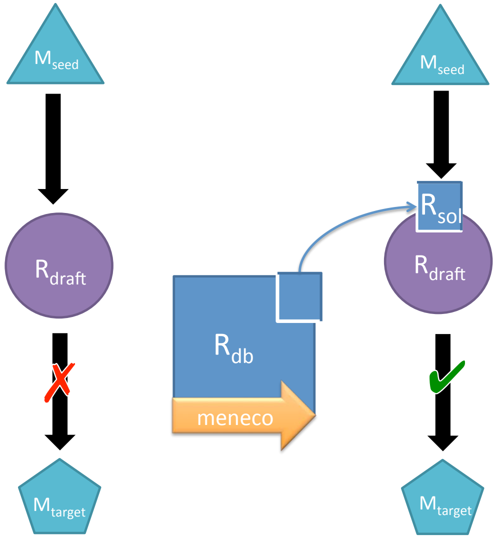


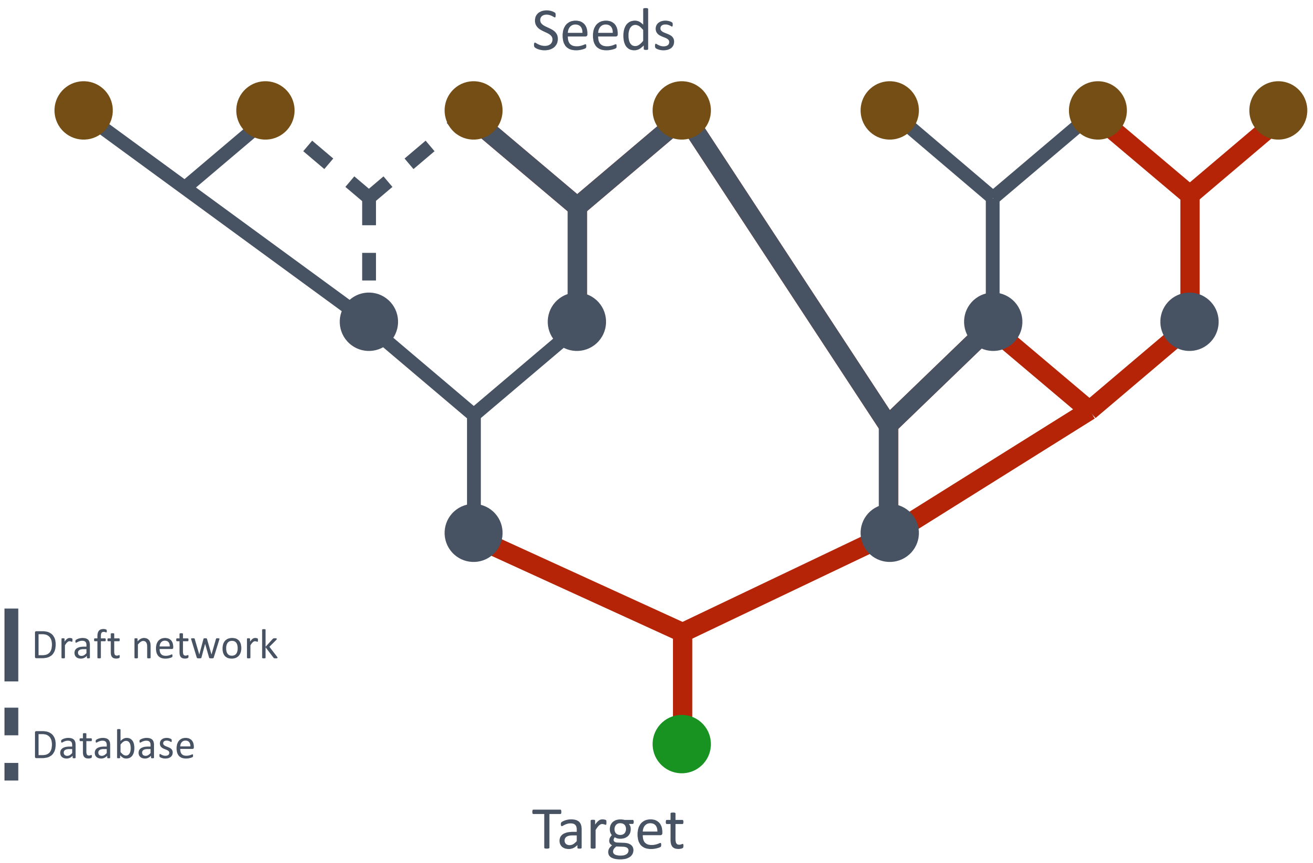
Gapfilling a metabolic network (nutshell)



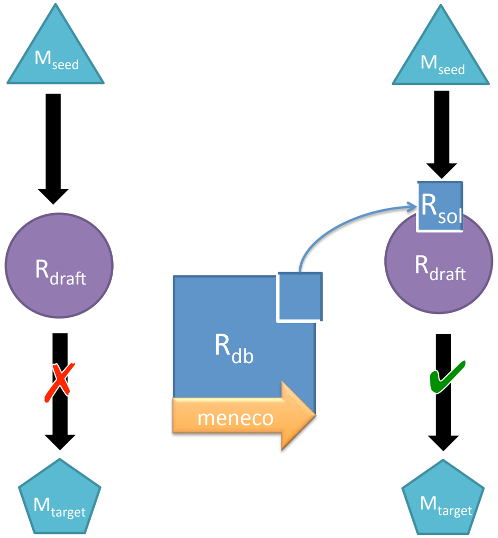


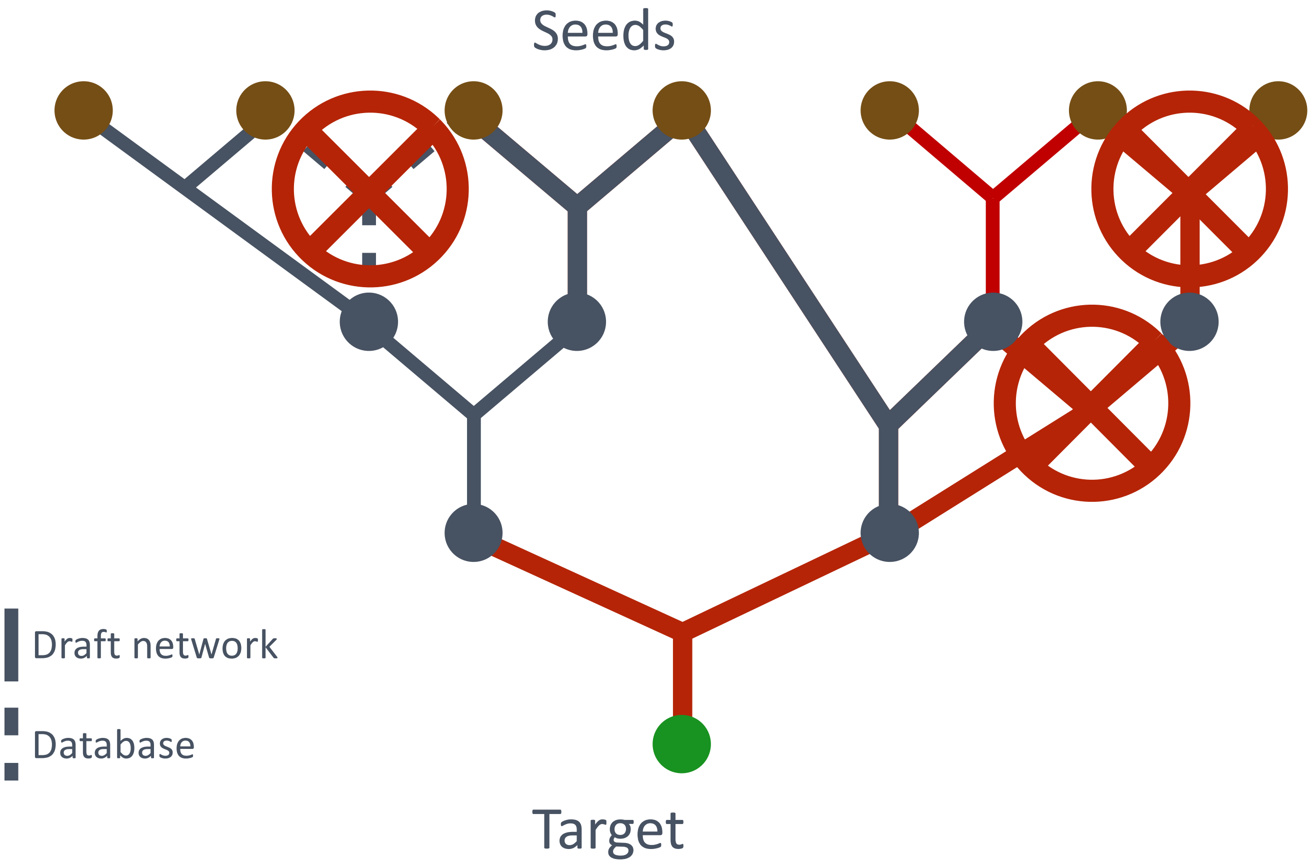
Gapfilling a metabolic network (nutshell)





Gapfilling a metabolic network (nutshell)

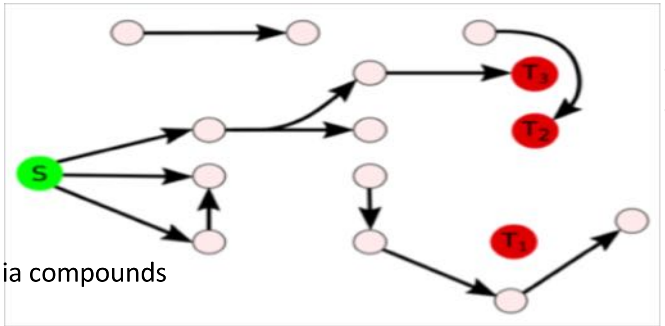




Gapfilling a metabolic network

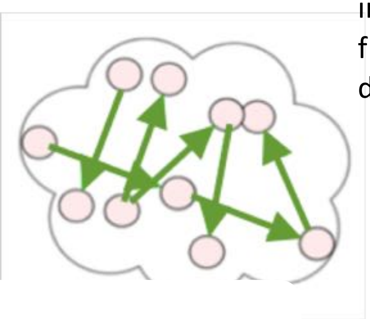
What we have

- Graph with **non-accessible target components**
- **Knowledge database** of possible edges



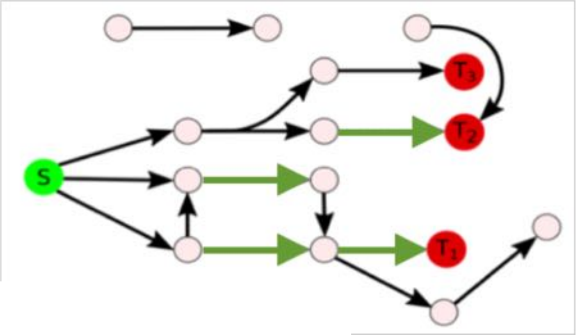
Experimentally observed compounds

Media compounds



Putative interactions from knowledge databases

Gap-filling problem:



- Restore target accessibility
- Minimal number of reactions

$$\mathrm{gapfilling}(\mathrm{S}, \mathrm{R_T}, \mathrm{G_1}, \mathrm{G_{DB}}) = \underset{\{R_i..R_m\} \subset G_{DB}}{\arg\min} \left(\begin{array}{c} size(reactants(R_T) \setminus scope(G_1 \cup \{R_i..R_m\}) \\ size\{R_i..R_m\} \end{array} \right)$$

Meneco: ASP-based gap-filling for non-model organisms

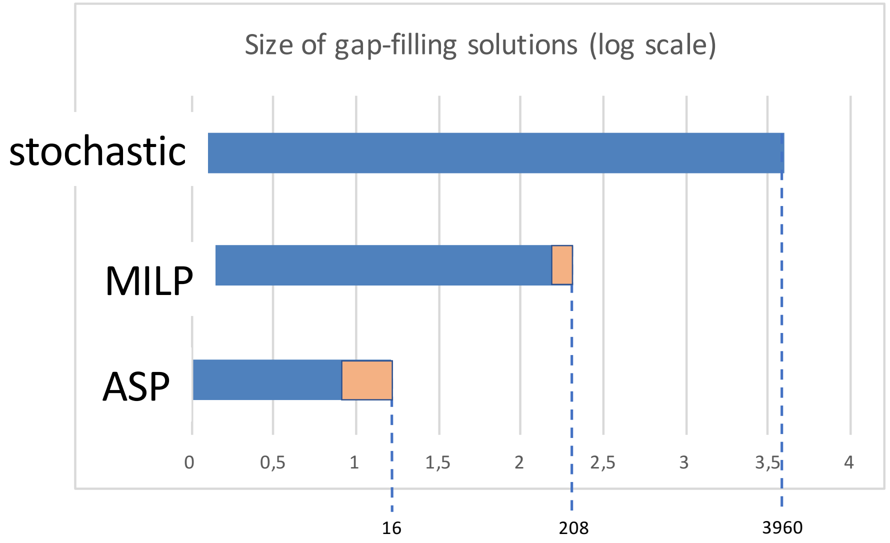
$$\mathrm{Hybgapfilling}(\mathrm{S}, \mathrm{R_T}, \mathrm{G_1}, \mathrm{G_{DB}})$$

$$\underset{\{R_i..R_m\}\subset G_{DB}}{\arg\min} \left(\begin{array}{c} size(reactants(R_T) \setminus scope(G_1 \cup \{R_i..R_m\})) \\ size\{R_i..R_m\} \end{array} \right)$$

```
{reaction(r)}.
scope(M):- seed(M).
scope(M):- product(M,R), reaction(R), scope(M′) : reactant(M′,R).
:- target(T), not scope(T).
#minimize{ reaction(r) }.
```

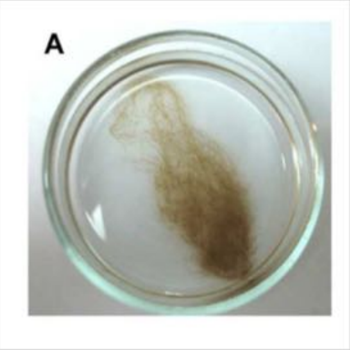
16 reactions in average are sufficient to restore degraded bacterial networks (PLOS CB 2017)

- ➢ MILP-based approaches required from 200 to 4000 reactions.



Benchmark of 10,800 bacterial networks

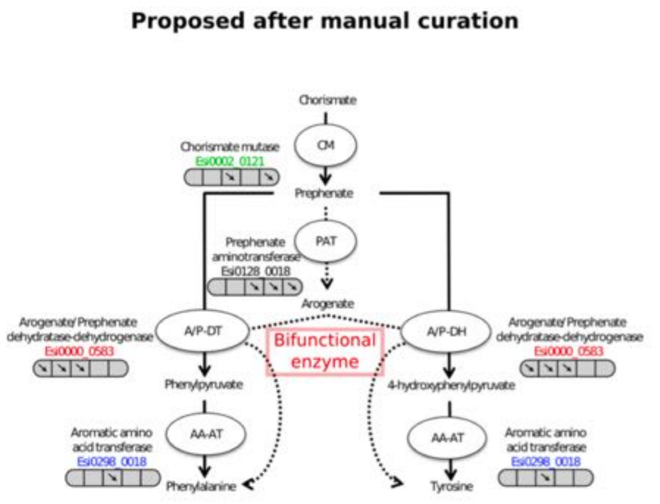
Example of application



Ectocarpus siliculosus

[Tapia2016]

- **Genome: 1785 reactions, 1981 compounds**
- **54 metabolites to produce:**
  - 25 are graph-based producible
  - None is FBA-based producible.
- **Gapfilling**
  - MILP : 500 reactions (untractable)
  - ASP: 50 reactions added to the network
    - Sufficient for fluxes
    - Manual curation



New bifunctional role of a specific enzym

(Plant Journal 2015)

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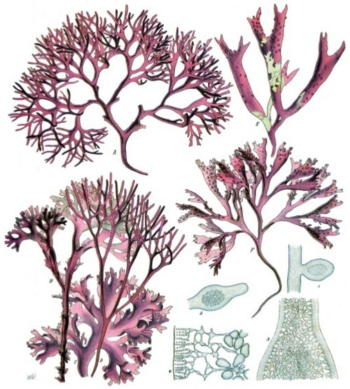
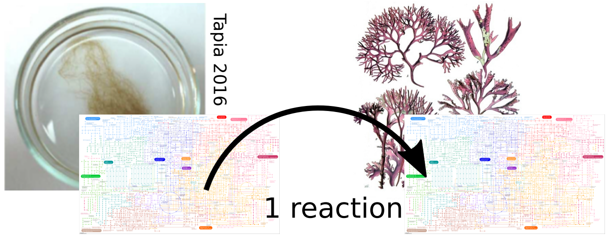
Counter-example of application



Chondrus crispus

Network analysis (G. Markov, SBR)

- 1943 reactions
- 149 reactions added by ASP
- **No way to produce biomass**

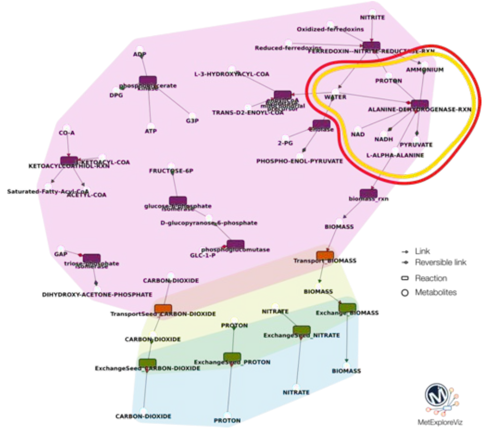


New problem to be solved

- **Hybrid problem** (TPLP 2018)
- Constraint propagator
- Reduce the database

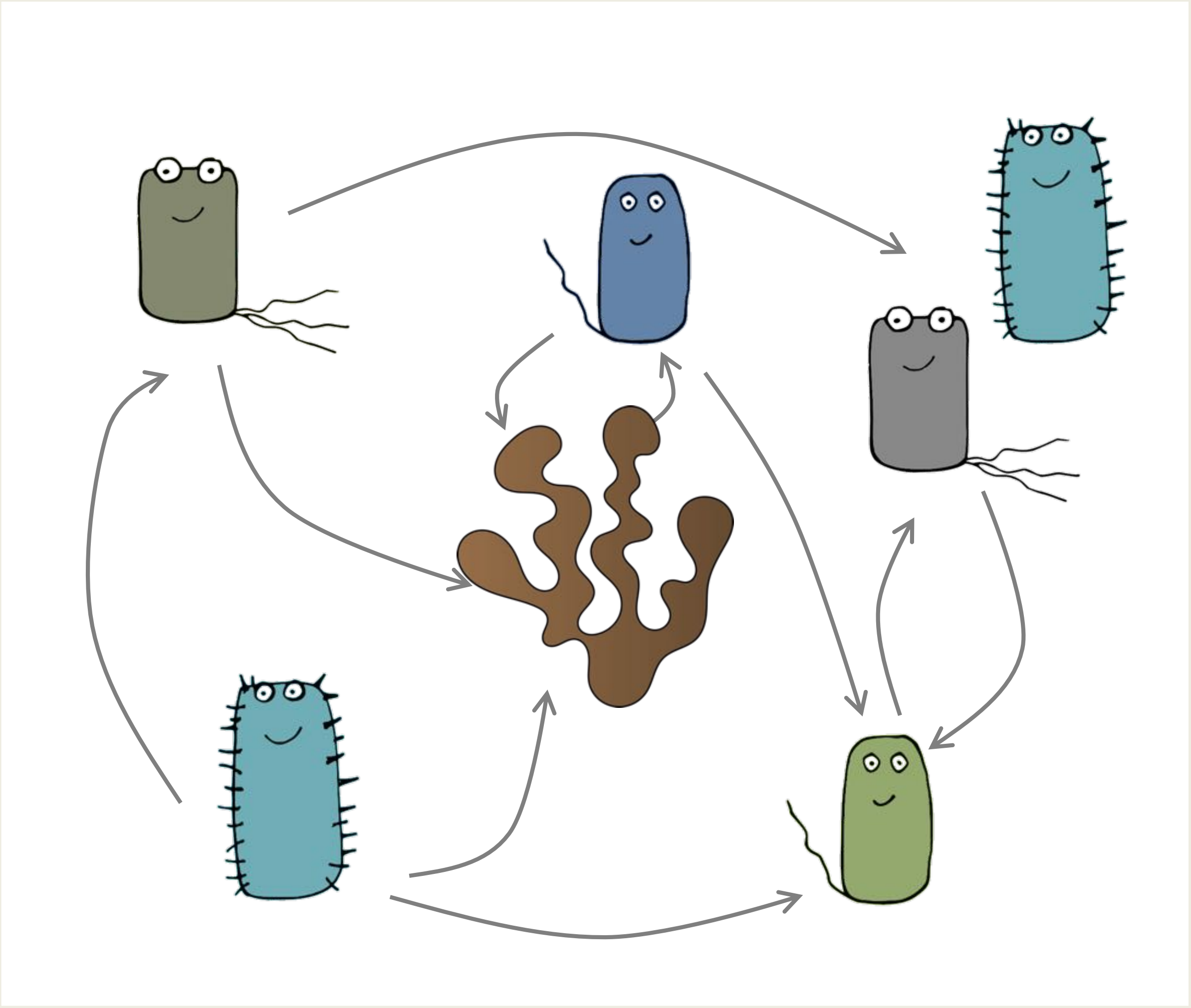
$$\mathrm{Hybgapfilling}(\mathrm{S}, \mathrm{R_T}, \mathrm{G_1}, \mathrm{G_{DB}}) = \underset{\{R_i..R_m\} \subset G_{DB}}{\arg\min} \left(\frac{size(reactants(R_T) \setminus scope(G_1 \cup \{R_i..R_m\})}{size\{R_i..R_m\}} \right)$$

$$\text{s.t} \quad s.v = 0, v_{R_T} > 0,\ lb < v < ub$$

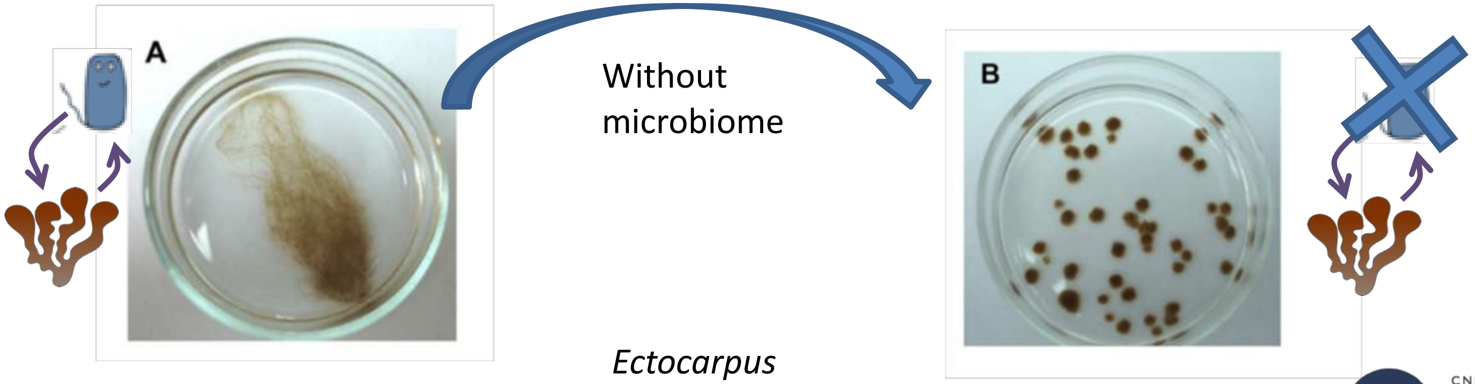


Essential reactions for alanine production in *CcrGem*

STILL MORE COMPLEXITY



Role of environmental bacteria ?



Without microbiome

Ectocarpus
[Dittami2014, Tapia2016, Prigent2015]

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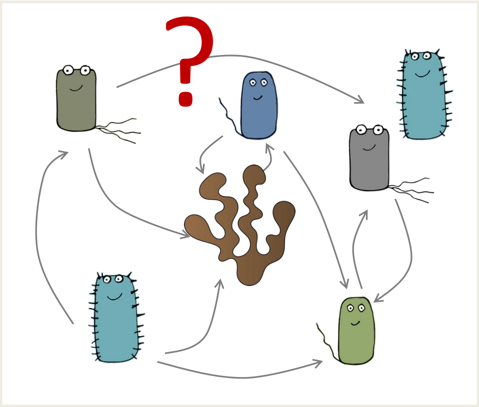
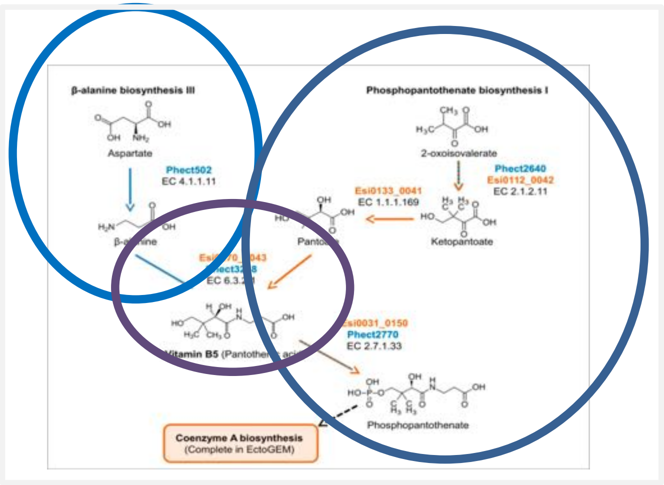
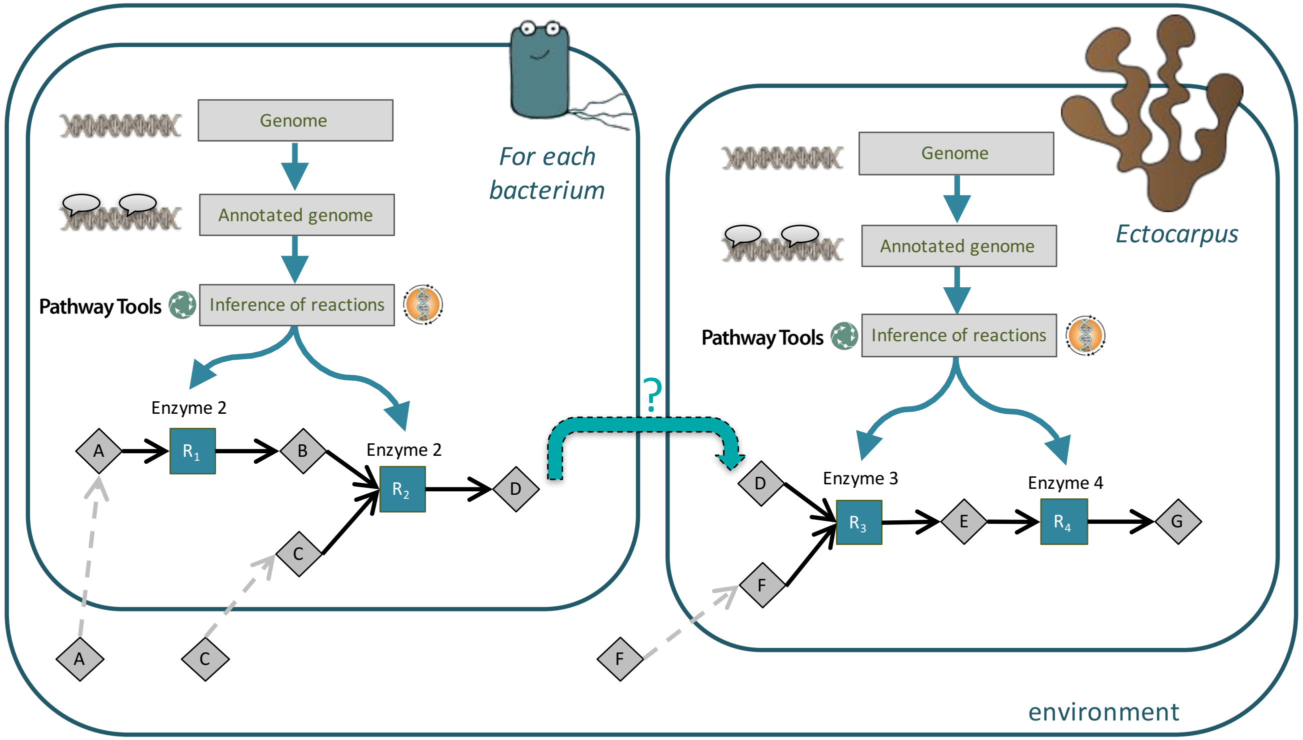




Metabolism may be an explanation

(PLOS CB 2017)

Systems ecology question

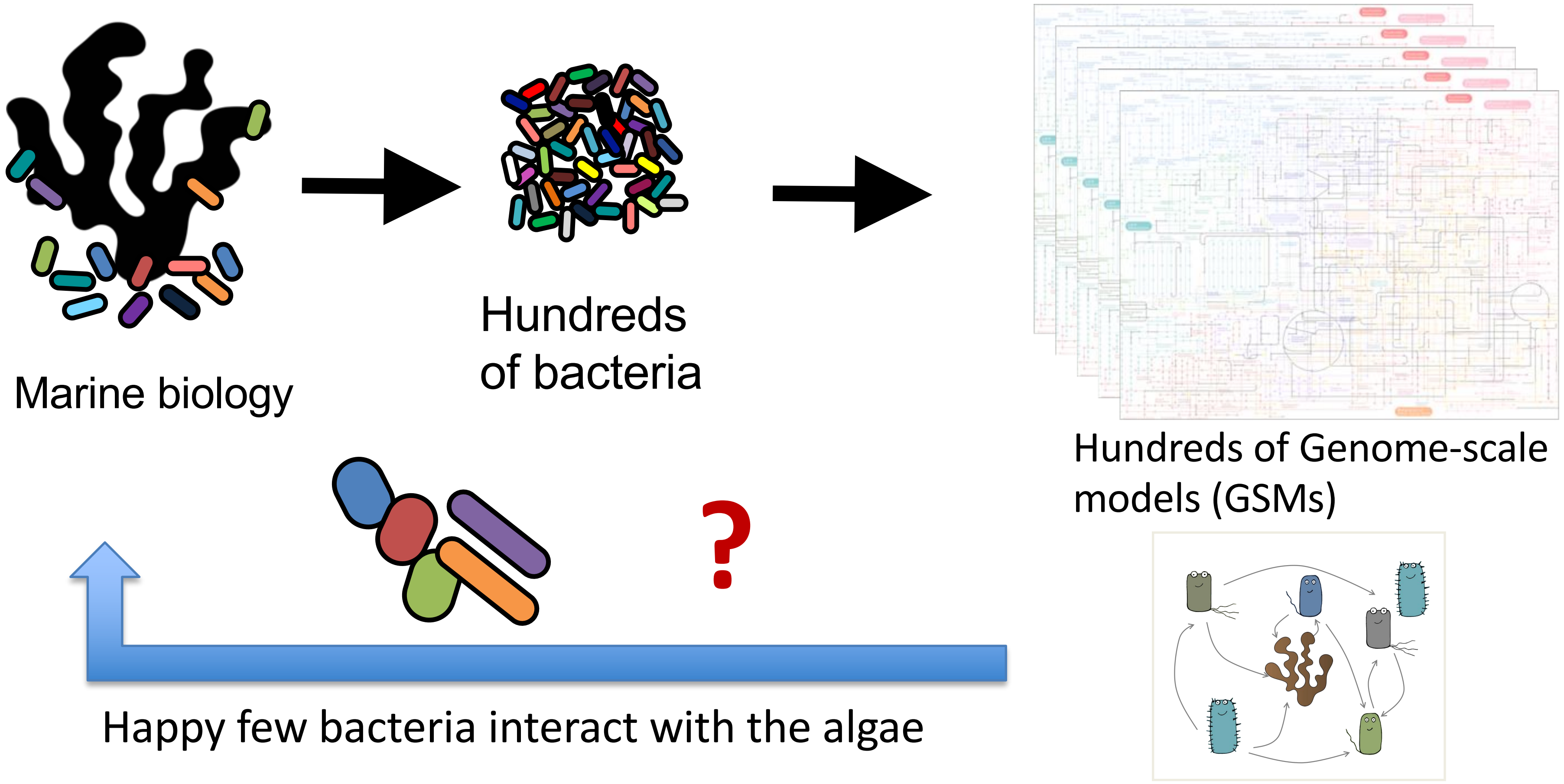


Can we suggest compound exchanges that could restore the production of targeted compounds ?

- New gap-filling problem !
- Steiner graph approach (Sagot team, 2017) or ASP implementation

Scalability…

But… There are hundreds of bacteria in the environment



Marine biology

Hundreds of bacteria

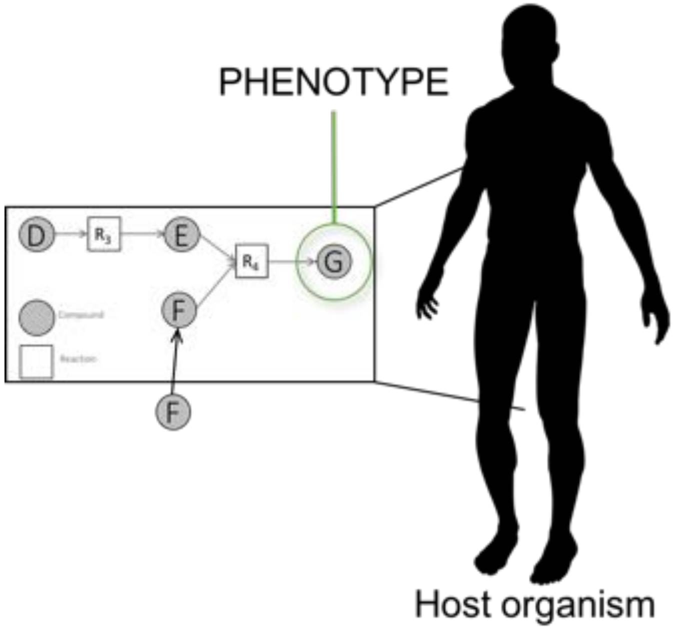
Hundreds of Genome-scale models (GSMs)

?

Happy few bacteria interact with the algae

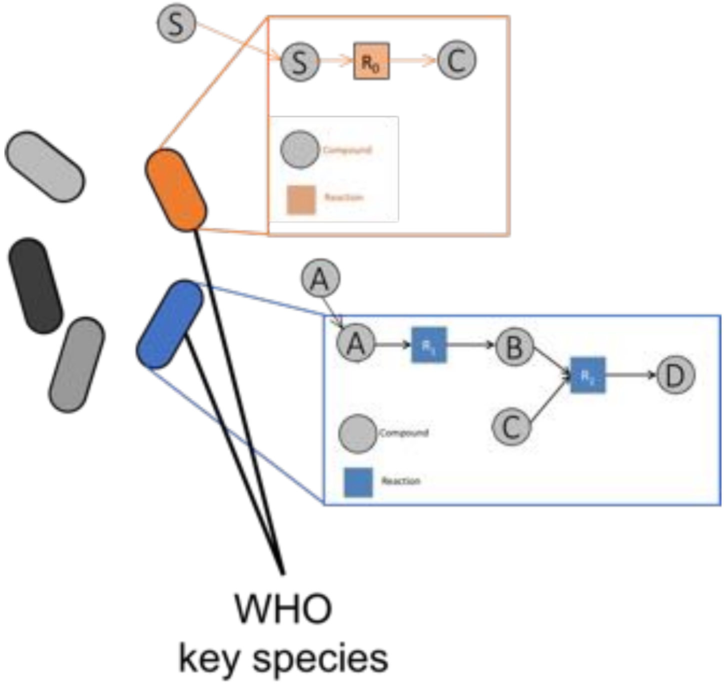
How to select communities within large microbiotas which explain the algal response to stress ?

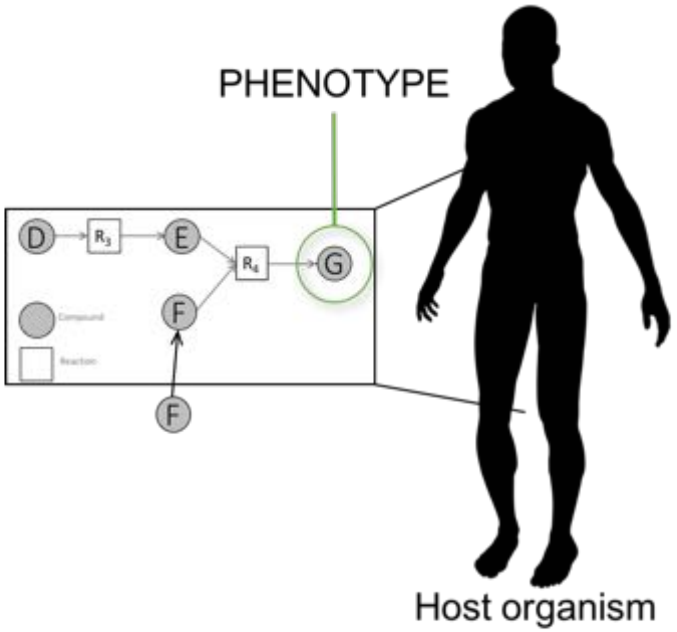
Selecting communities of interest within [large] microbiotas



The “who”, “how” challenges of community selection

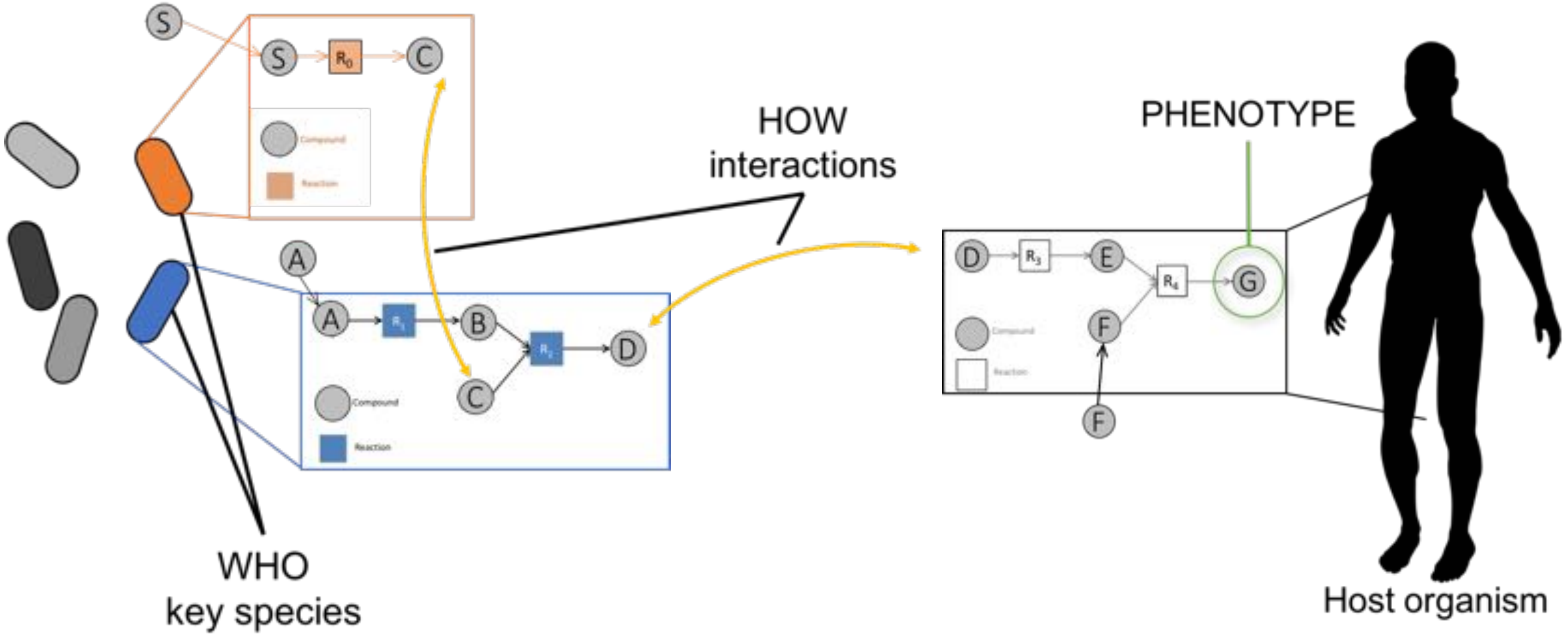
Selecting communities of interest within [large] microbiotas





The "who", "how" challenges of community selection

Selecting communities of interest within [large] microbiotas



The “who”, “how” challenges of community selection

Complexity

Community selection problem

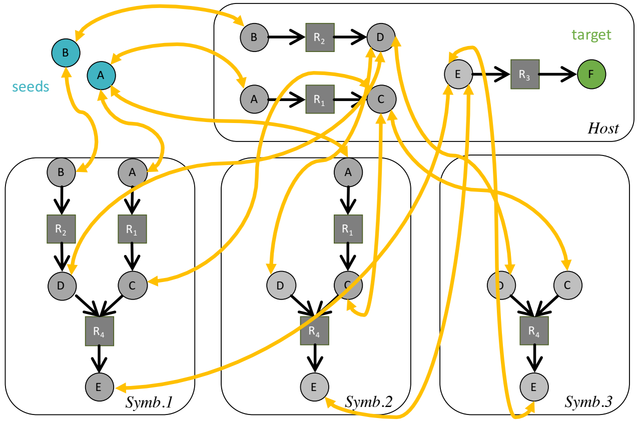
- ➢ Switch from hundreds of symbiots to 3 or 4
- ➢ Pinpoint a few number of putative cross-feedings

$$\mathrm{Comsel}(S,T,G_1..G_n) = \underset{\{exchg(G_{i_1}..G_{i_L})\}\subset\{G_1..G_n\}}{\arg\min} \begin{pmatrix} size(T \setminus MBscope(G_{i_1}..G_{i_L})) \\ \\ size\{\varepsilon \subset exchg(G_{i_1}..G_{i_L}) \mid \\ T \cap CPscope(G_{i_1}..G_{i_L},\varepsilon,S) = \\ T \cap MBscope(G_{i_1}..G_{i_L},S)\} \end{pmatrix}$$

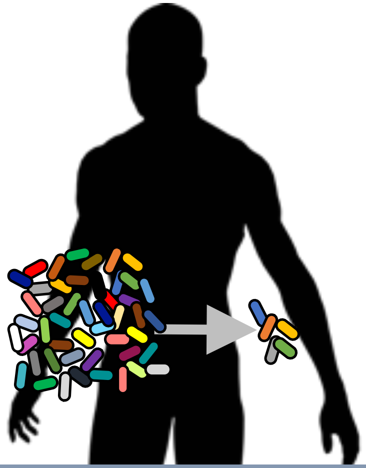
- ➢ depends on the number of hyperarcs

Size of the search space

- ➢ depends on the number of symbionts



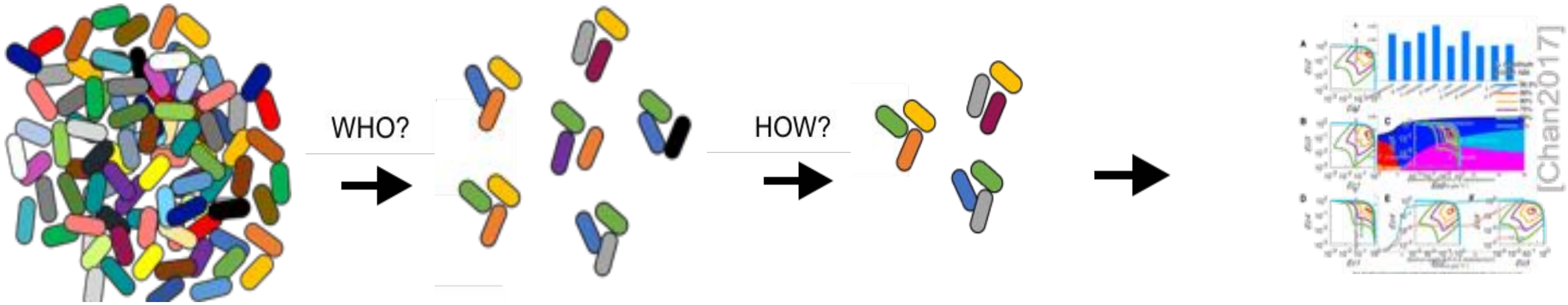
499,177 combinations of <6 exchanges



$1.62.10^{81}$ combinations of <10 exchanges

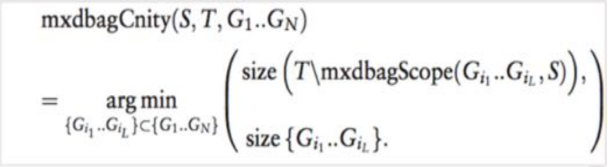
Highly combinatorial problem

Two-step optimization procedure



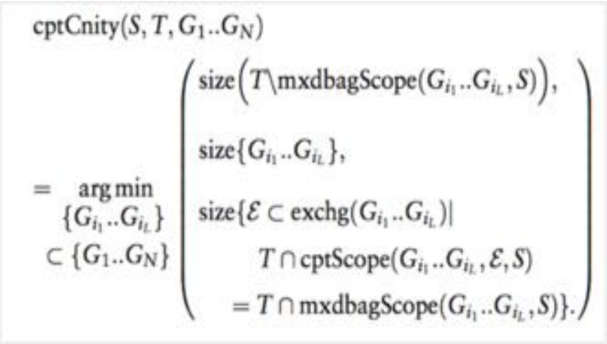
Heuristics for the community selection problem

- **Who problem.**
  - Get rid of boundaries and select all minimal symbiot families



$$\begin{aligned}&\mathrm{mxdbagCnity}(S,T,G_1..G_N)\\ &= \underset{\{G_{i_1}..G_{i_L}\}\subset\{G_1..G_N\}}{\arg\min}\begin{pmatrix}\mathrm{size}\left(T\backslash\mathrm{mxdbagScope}(G_{i_1}..G_{i_L},S)\right),\\ \mathrm{size}\,\{G_{i_1}..G_{i_L}\}.\end{pmatrix}\end{aligned}$$

- **How problem.**
  - Sort the selected families according to the number of exchanges

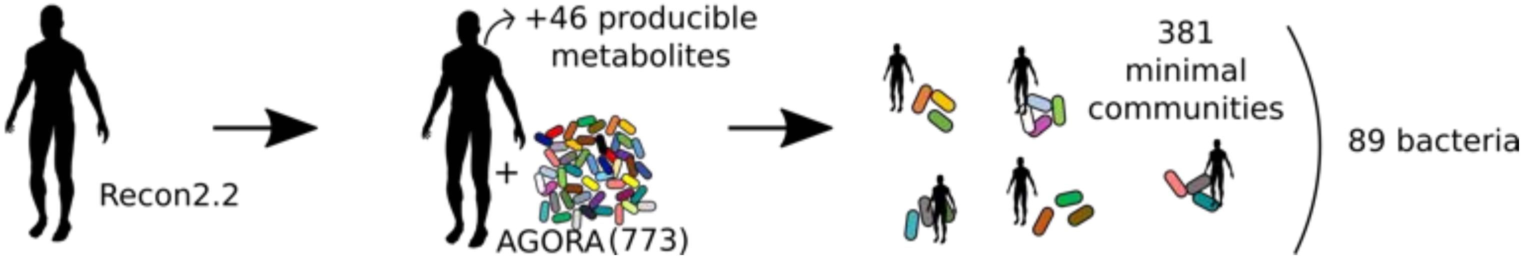


$$\begin{aligned}&\mathrm{cptCnity}(S,T,G_1..G_N)\\ &= \underset{\substack{\{G_{i_1}..G_{i_L}\}\\ \subset\{G_1..G_N\}}}{\arg\min}\begin{pmatrix}\mathrm{size}\left(T\backslash\mathrm{mxdbagScope}(G_{i_1}..G_{i_L},S)\right),\\ \mathrm{size}\{G_{i_1}..G_{i_L}\},\\ \mathrm{size}\{\mathcal{E}\subset\mathrm{exchg}(G_{i_1}..G_{i_L})|\\ \quad T\cap\mathrm{cptScope}(G_{i_1}..G_{i_L},\mathcal{E},S)\\ \quad =T\cap\mathrm{mxdbagScope}(G_{i_1}..G_{i_L},S)\}.\end{pmatrix}\end{aligned}$$

- **Manual curation.**
  - Ask your favorite biologist to select the final one

Validation/benchmarking on human microbiome project

Context of the study [Swainston et al., 2016] [Magnúsdóttir et al., 2016]



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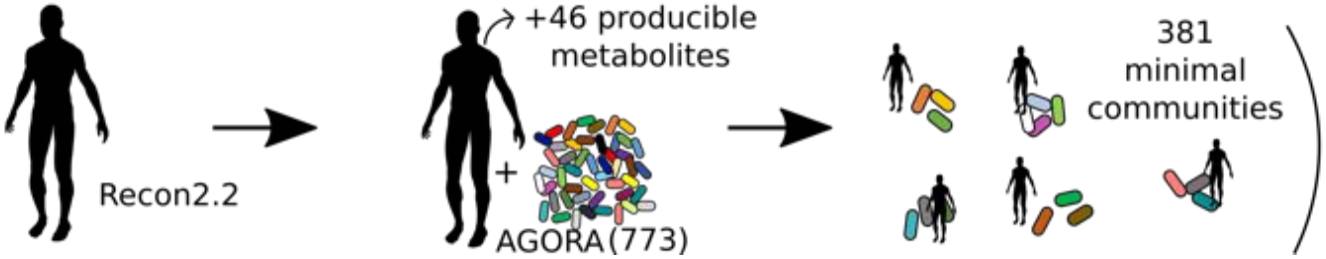
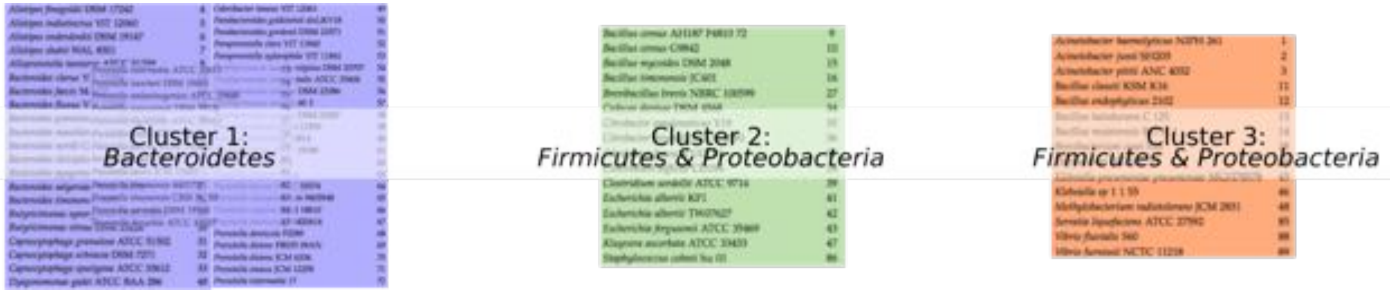


89 bacteria

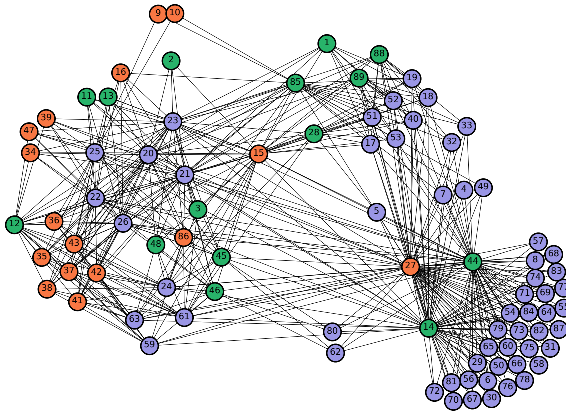
Clustering of bacteria


Cluster 1: *Bacteroidetes*
Cluster 2: *Firmicutes & Proteobacteria*
Cluster 3: *Firmicutes & Proteobacteria*

Alistipes finegoldii DSM 17242	4	*Odoribacter laneus YIT 12061*	49
Alistipes indistinctus YIT 12060	5	*Parabacteroides goldsteinii dnLKV18*	50
Alistipes onderdonkii DSM 19147	6	*Parabacteroides gordonii DSM 23371*	51
Alistipes shahii WAL 8301	7	*Paraprevotella clara YIT 11840*	52
Alloprevotella tannerae ATCC 51259	8	*Paraprevotella xylaniphila YIT 11841*	53
[illegible]	[illegible]	[illegible]	[illegible]
Capnocytophaga granulosa ATCC 51502	31	*Prevotella denticola F0289*	68
Capnocytophaga ochracea DSM 7271	32	*Prevotella disiens FB035 09AN*	69
Capnocytophaga sputigena ATCC 33612	33	*Prevotella disiens JCM 6336*	70
Dysgonomonas gadei ATCC BAA 286	40	*Prevotella oralis JCM 12251*	71

Bacillus cereus AH187 F4810 72	9
Bacillus cereus G9842	10
Bacillus mycoides DSM 2048	15
Bacillus timonensis JC401	16
Brevibacillus brevis NBRC 100599	27
Cedecea davisae DSM 4568	34
[illegible]	[illegible]
Clostridium sordellii ATCC 9714	39
Escherichia albertii KF1	41
Escherichia albertii TW07627	42
Escherichia fergusonii ATCC 35469	43
Kluyvera ascorbata ATCC 33433	47
Staphylococcus cohnii hu 01	86

Acinetobacter haemolyticus NIPH 261	1
Acinetobacter junii SH205	2
Acinetobacter pittii ANC 4052	3
Bacillus clausii KSM K16	11
Bacillus endophyticus 2102	12
[illegible]	[illegible]
Klebsiella sp 1 1 55	46
Methylobacterium radiotolerans JCM 2831	48
Serratia liquefaciens ATCC 27592	85
Vibrio fluvialis 560	88
Vibrio furnissii NCTC 11218	89



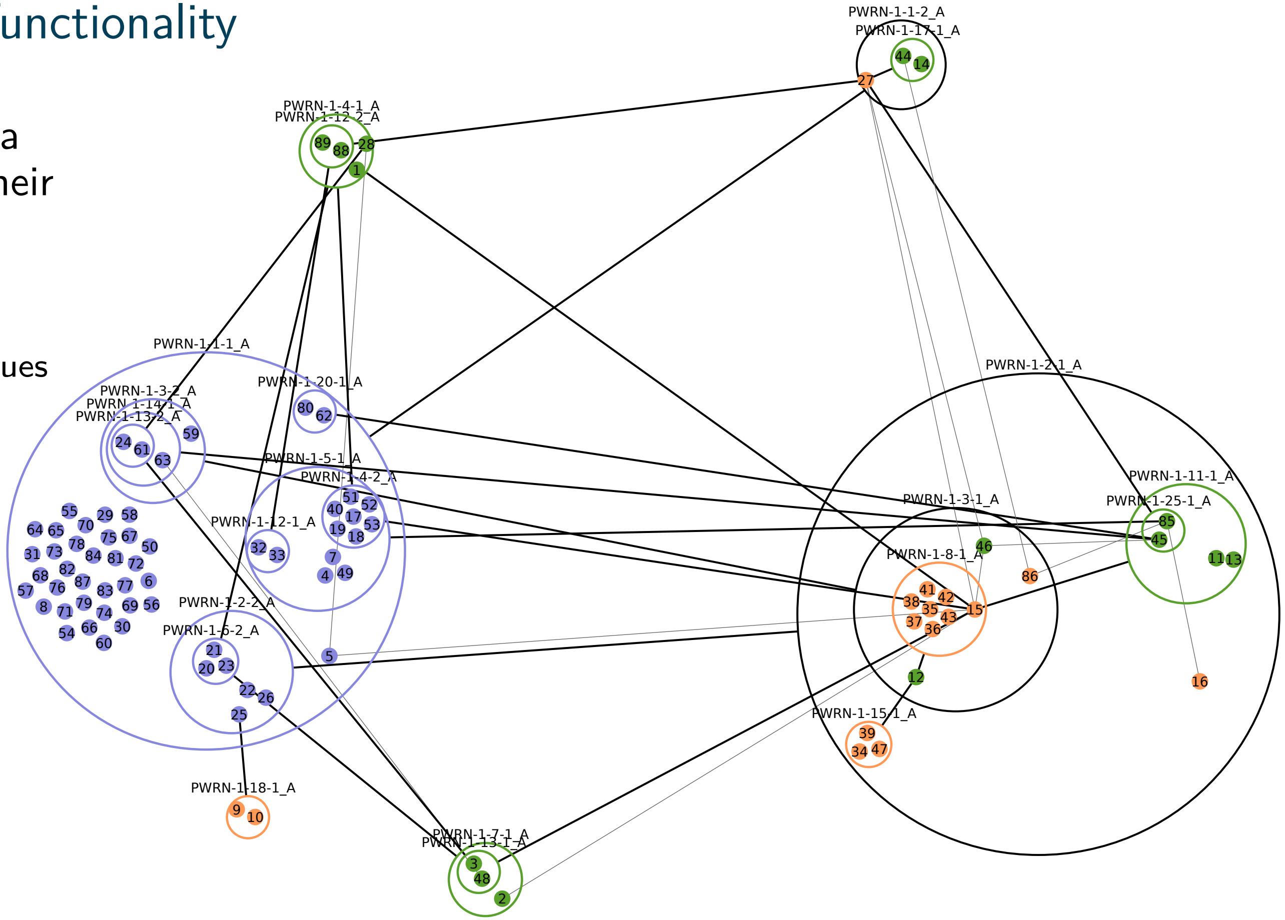
Each of the 381 communities is composed of
1 *Bacteroidetes* (/58) + 1 *Firmicute* or *Proteobacteria* (/15) + 1 *Firmicute* or *Proteobacteria* (/16)

C. Frioux's Thesis. ECCB 2018

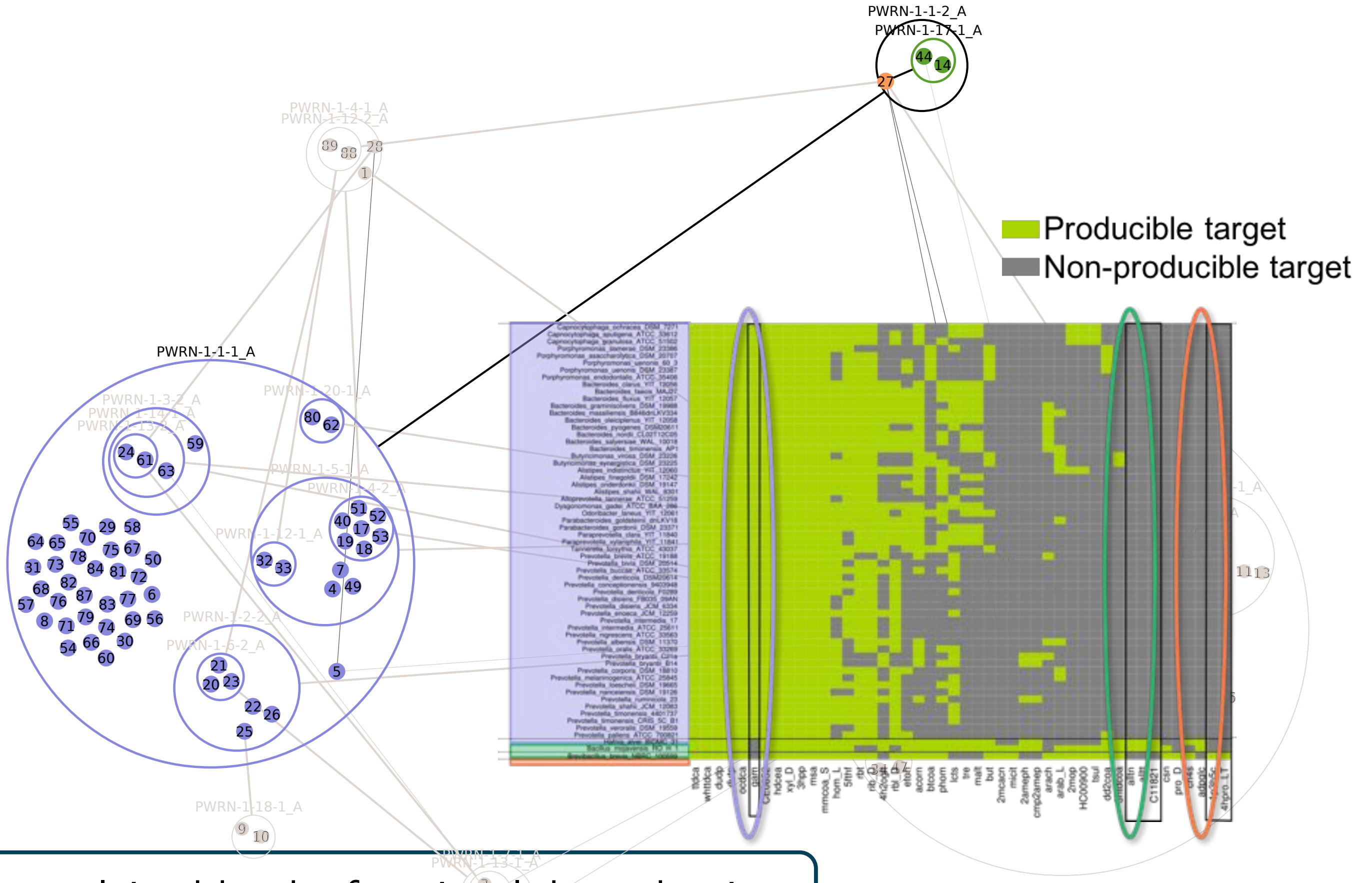
Validation/benchmarking on human microbiome project

Association of bacteria & functionality

- Groups of equivalent bacteria in clusters with respect to their associations [Bourneuf et al., 2017]
  - **Powernodes:** groups of bacteria, parts of bicliques
  - **Poweredges:** connect bicliques



Validation/benchmarking on human microbiome project



- Producibility of individual targets explains the communities → screening

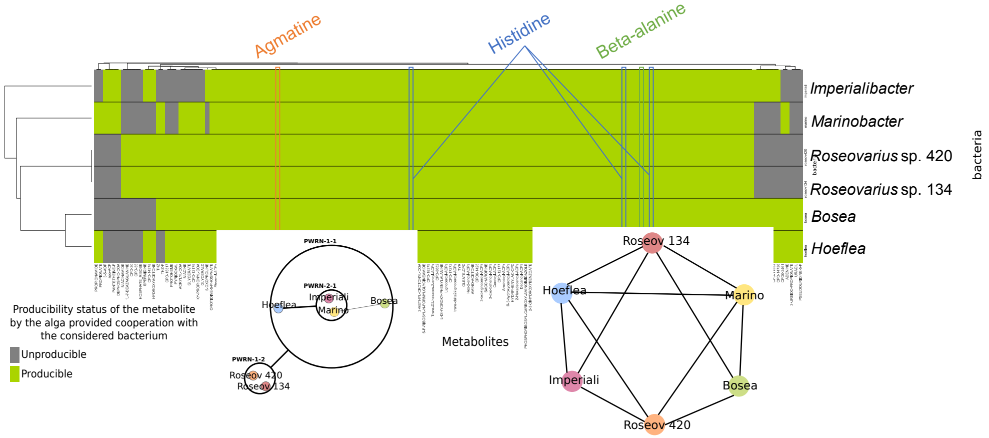
Community composition can be explained by the functional dependencies of the targets towards specific groups of bacteria

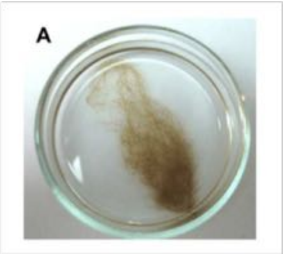
C. Frioux's Thesis. ECCB 2018

Validation/benchmarking on human microbiome project

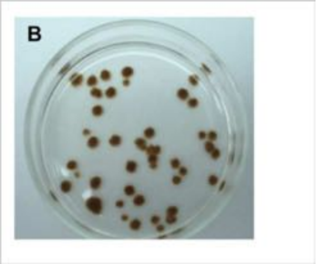
- *Ca.* P. ectocarpi not culturable
- 10 culturable bacteria → functional redundancy
- 6 equivalent communities of 3 bacteria

Joint work with Enora Fremy, Bertille Burgunter-Delamare & Simon Dittami

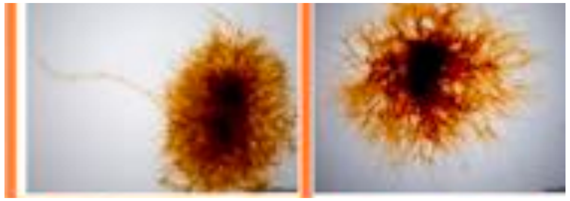




Without microbiome



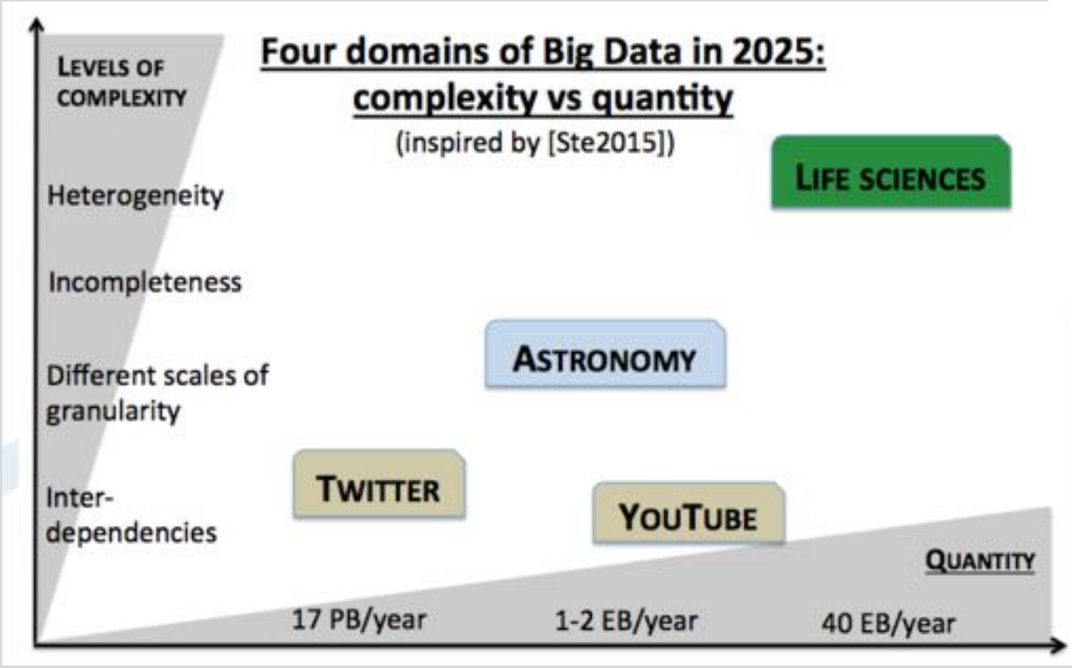
+ 3 selected bacteria among 30 cultivable bacteria



S. Dittami,
Bertille Burgunter-Delamare

The algae grew again… But with strange behaviors

TOWARDS CONCLUSION



Take home messages: life science data integration ?

- **Life science data are multi-scale and heterogeneous**
  - Linked by underlying regulatory processes

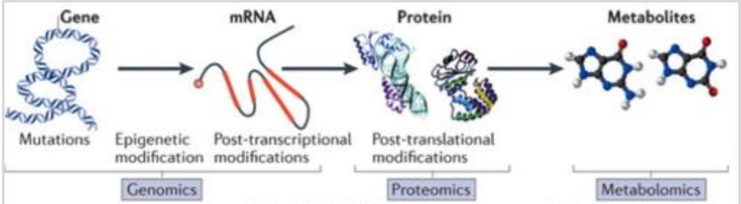
- **Systems biology ?**
  - study of complex systems which cannot be uniquely identified

- **Handling complexity for**
  - Make (dynamical) hypotheses
  - Solve optimization problems instead of identify parameters
  - Win-win collaboration with your BFF ASP-tech developers

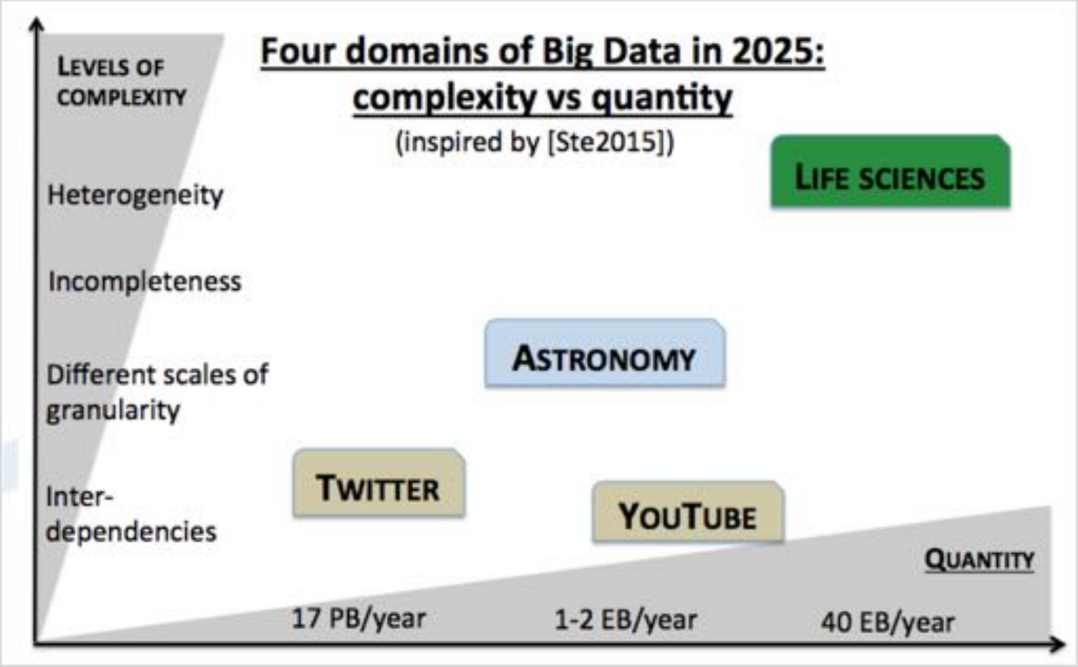
- **We will never replace biologists**

Molecular and cellular life science analysis is a user-assisted data science rather than a modeling system science

What about the future



Patti et al. (2012). Metabolomics: the apogee of the omics trilogy. Nature


Four domains of Big Data in 2025: complexity vs quantity

(inspired by [Ste2015])

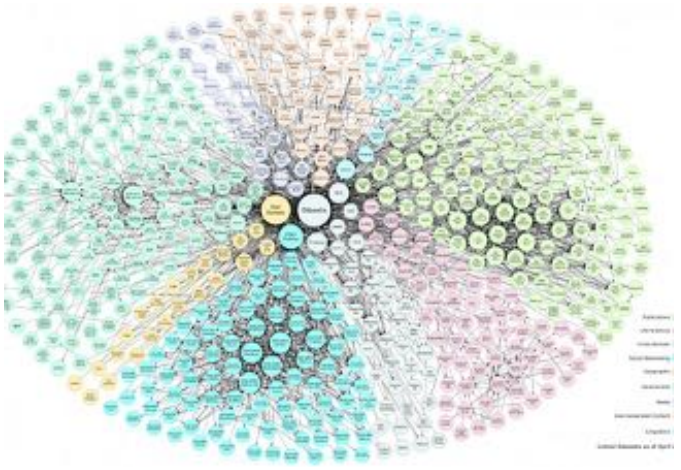
- **Size complexity**
  - Towards deep-learning ?

- **Heterogeneity complexity ?**
  - Knowledge-based methods

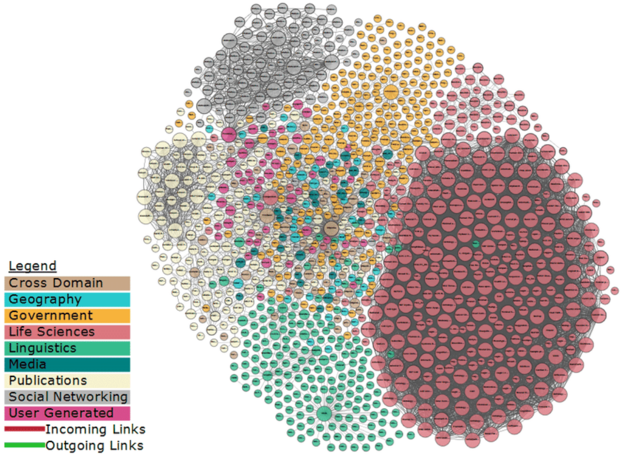
Linked open data

- **More than 1500 life science databases**
  - Gene Ontology
  - Chebi
  - KEGG
  - Swissprot…

- **Many of these DB are being linked and can be queried**
  - **Huge knowledge repositories to support reasoning**



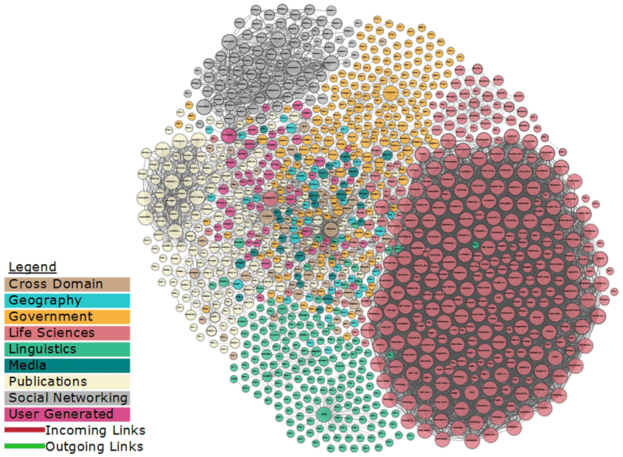
Linked Open Data initiative (2014)



Linked Open Data initiative (2017)

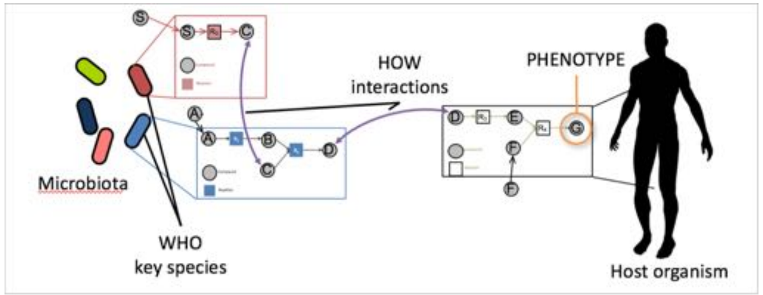
The futur of life-science data analysis ?

Machine learning : compound, function and species identification



Knowledge representation : Connect data

- Performant queries
- User-friendly interfaces



Formal approaches : explain

- Automatic reasoning
- **Assist biologists and never replace them**

Prospective

- **Our future role : facilitate and scale life science data analysis**
  - Easy exploration of search spaces
  - **Extract dynamical features as constraints** (temporal ?)
  - Use knowledge DBs

- **Always explain the results**
  - Give choices to experimentalists
  - **According to all the hypotheses that we make, biologists have to double-check our predictions.**

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