

Omics data analysis in genome scale metabolic networks

Summer school Multi-omics - Aussois
Jean-Clément Gallardo
07 / 09 / 2023

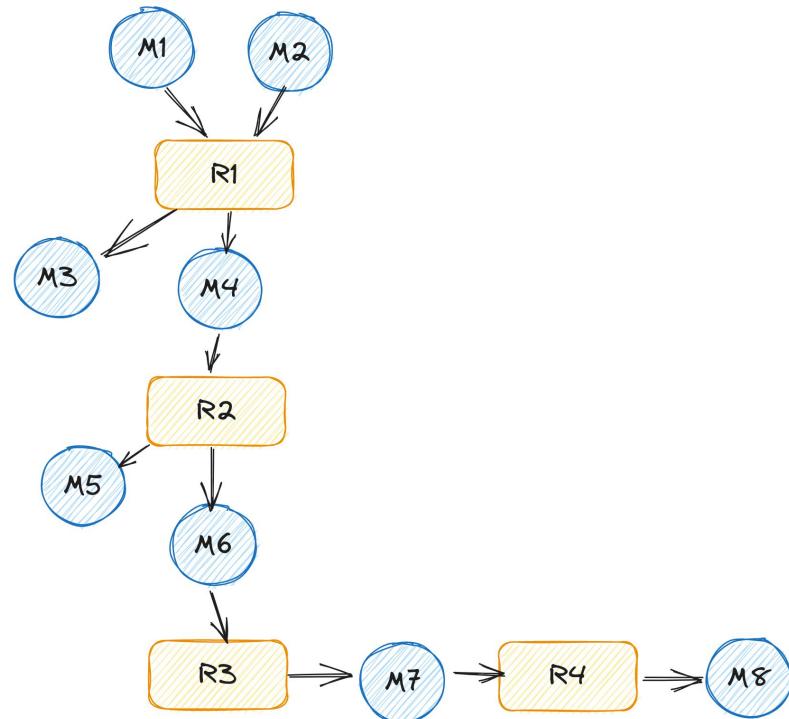


Metabolic networks

A definition of a metabolic network

A metabolic network is:

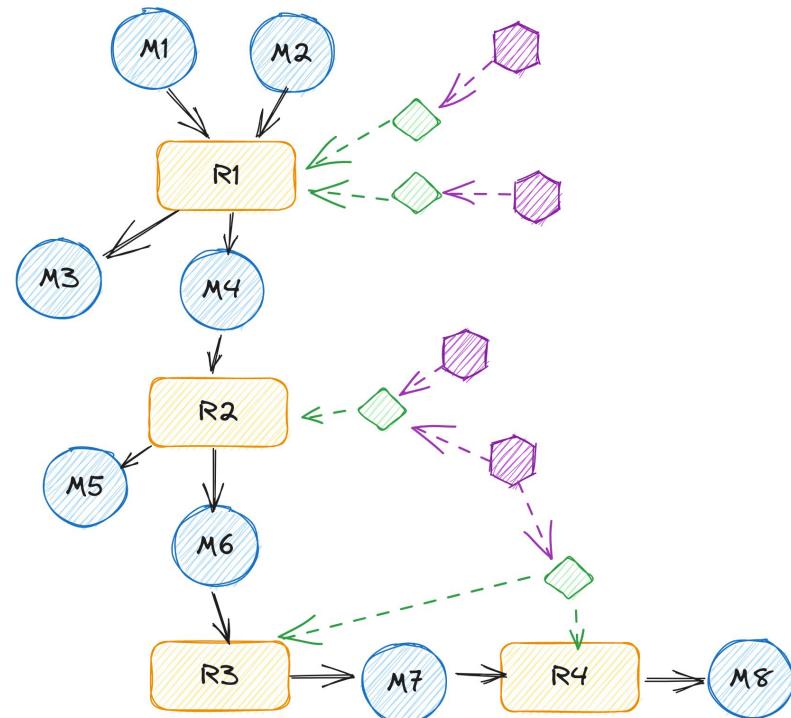
- a set of biochemical reactions linked together by the metabolites that they consume and produce



A definition of a metabolic network

A metabolic network is:

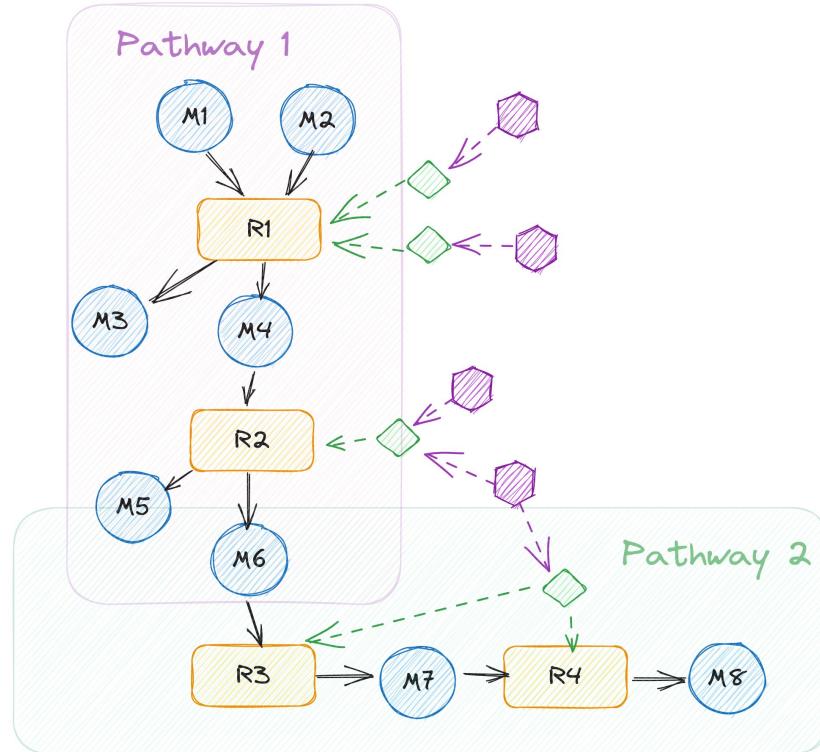
- a set of biochemical reactions linked together by the metabolites that they consume and produce
- the set of the genes that code for the enzymes that catalyse the reactions



A definition of a metabolic network

A metabolic network is:

- a set of biochemical reactions linked together by the metabolites that they consume and produce
- the set of the genes that code for the enzymes that catalyse the reactions
- the set of pathways where the reactions are involved

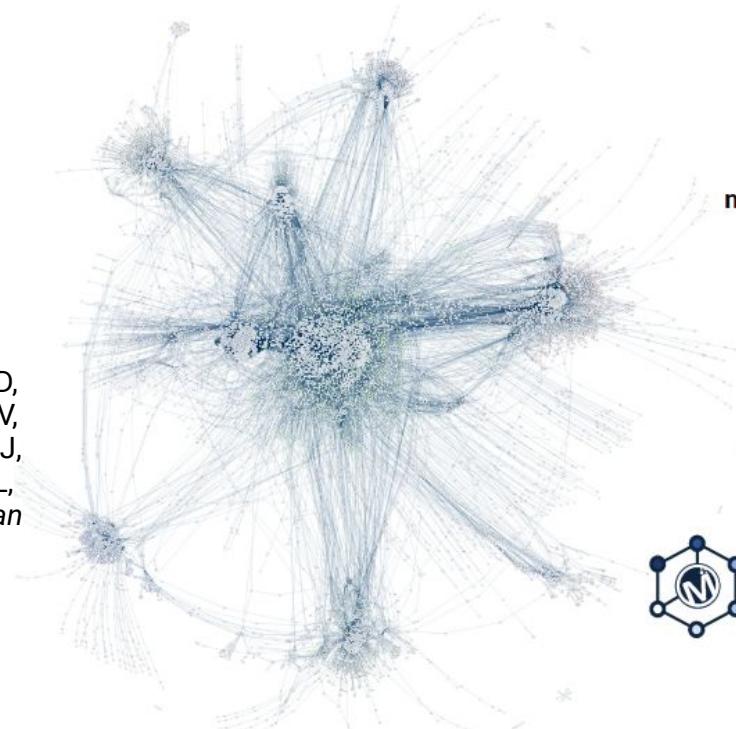


A definition of a genome-scale metabolic network

A metabolic network known to take place in
a target organism

Human-GEM
13024 reactions
8363 metabolites
2920 genes

Robinson JL, Kocabas P, Wang H, Cholley PE, Cook D, Nilsson A, Anton M, Ferreira R, Domenzain I, Billa V, Limeta A, Hedin A, Gustafsson J, Kerkhoven EJ, Svensson LT, Palsson BO, Mardinoglu A, Hansson L, Uhlén M, Nielsen J, 2020. *An atlas of human metabolism*. Science signaling



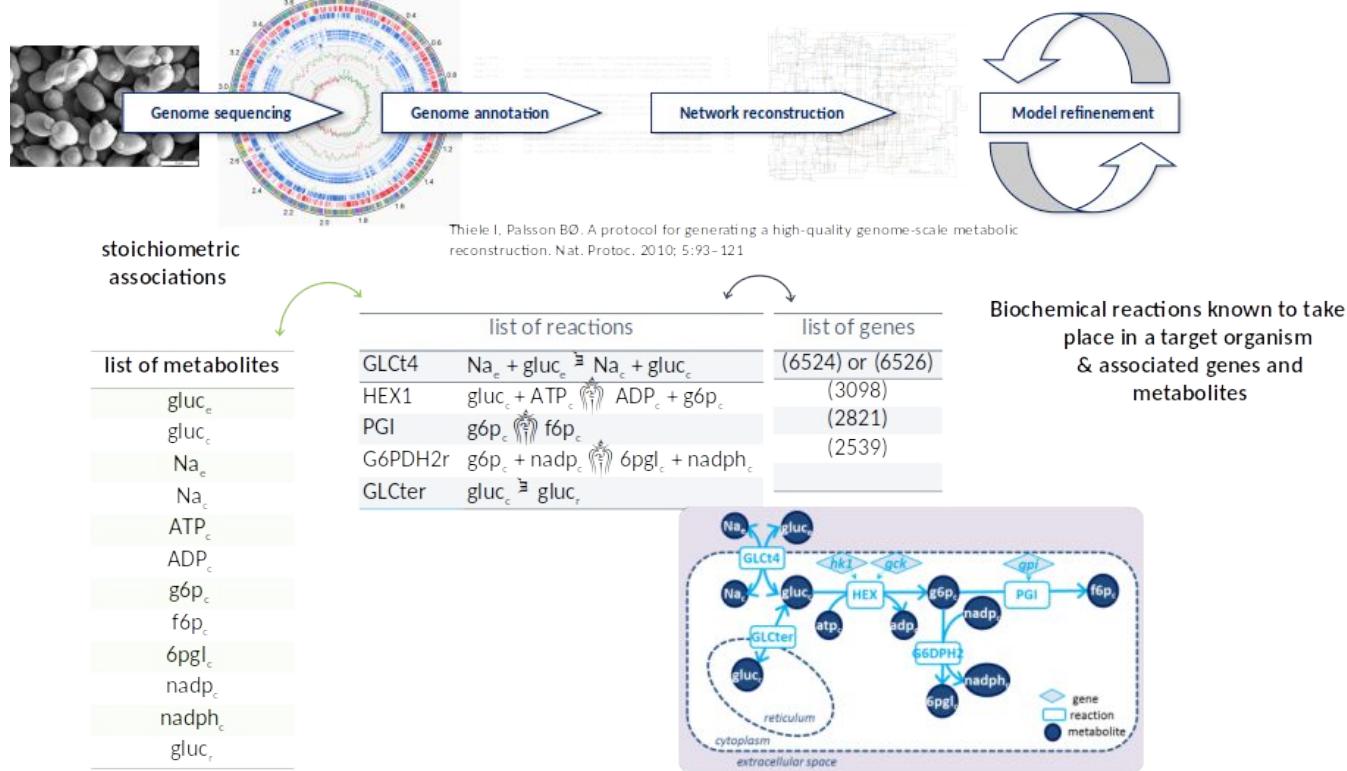
**human genome-scale
metabolic reconstruction Recon2.2**
7785 reactions
2652 metabolites
1675 genes
Swainston N. et al. Metabolomics. 2016.



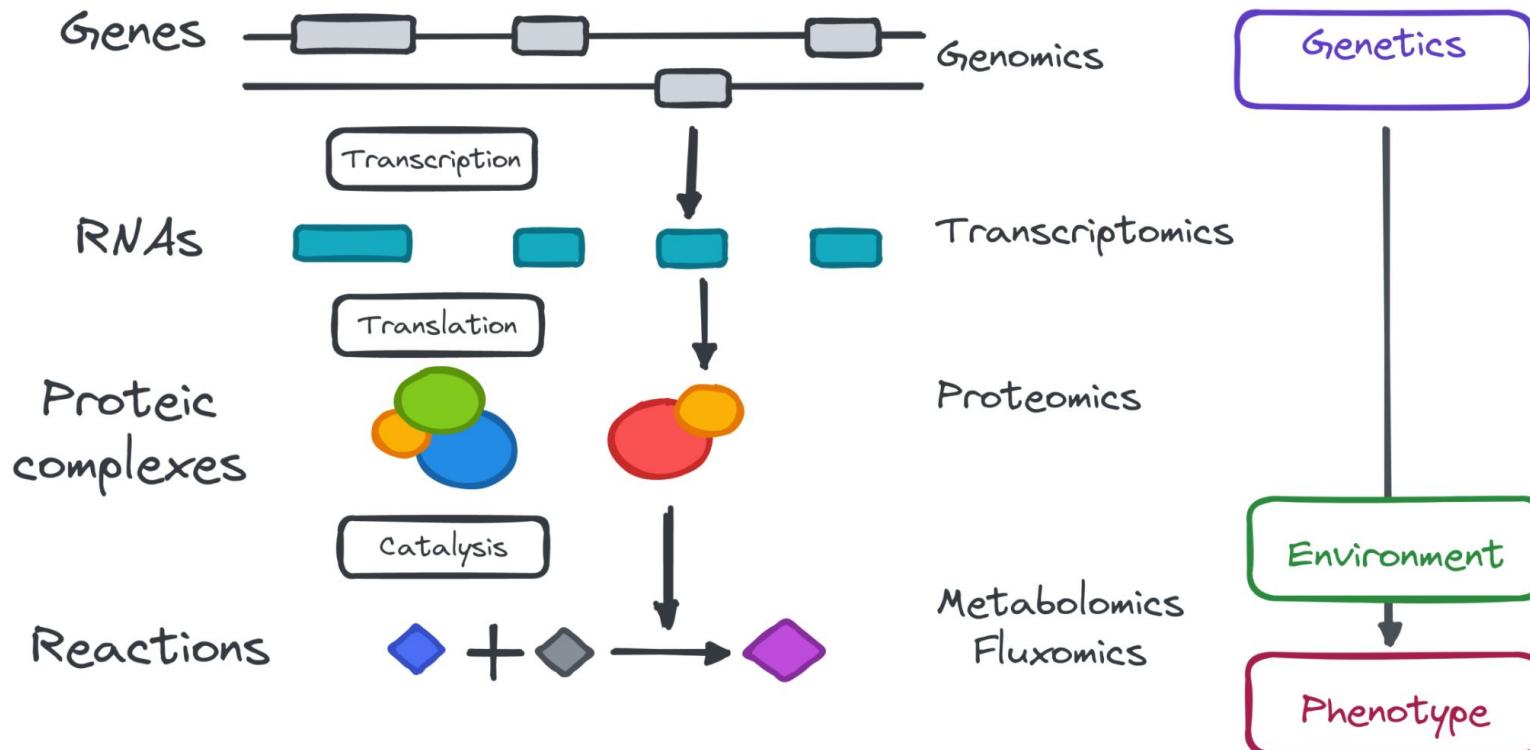
Genome-scale metabolic reconstructions

Build from its genome annotation.

- Infer catalytic activities from comparisons between sequences of target genes and genes of model organisms
- Deduced list of reactions that can potentially take place in the target organism
- Associated metabolites from reactions

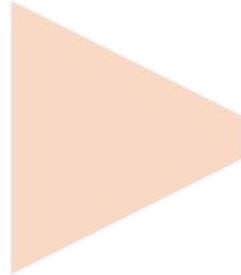


The metabolic network: a context of interpretation for omics data

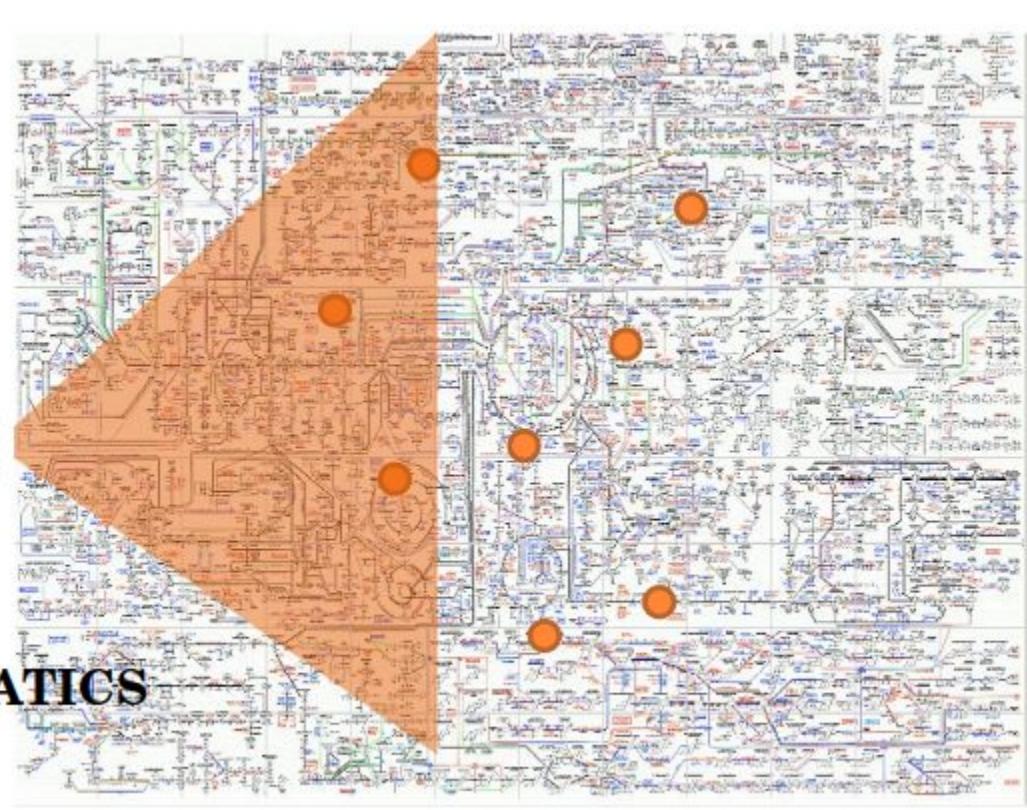


Mapping omics data

OMICS
DATA



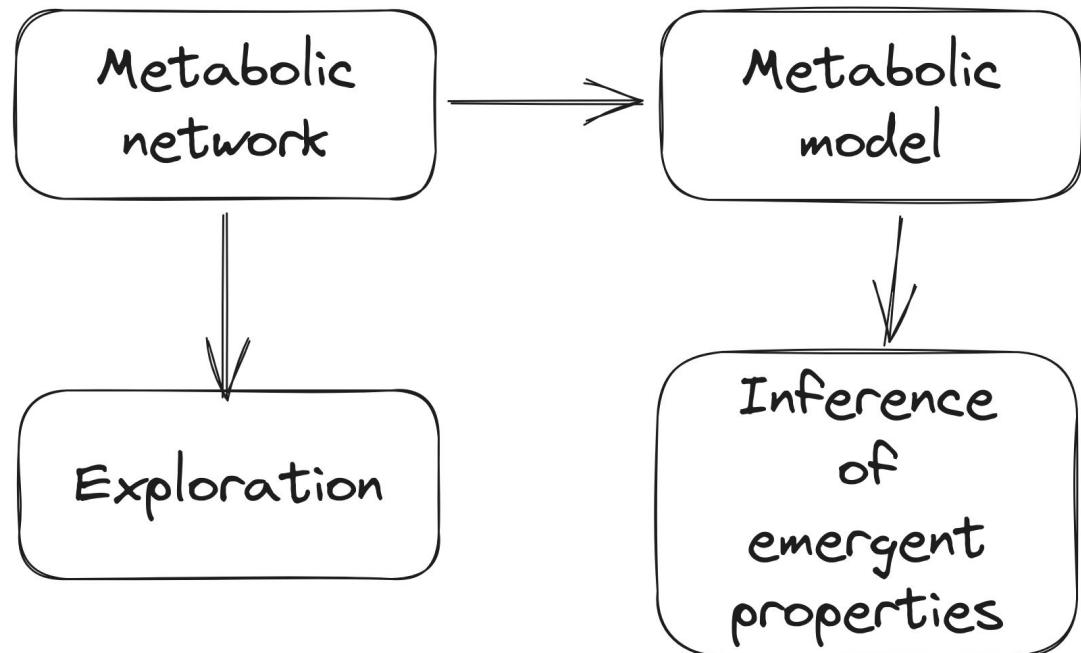
BIOINFORMATICS



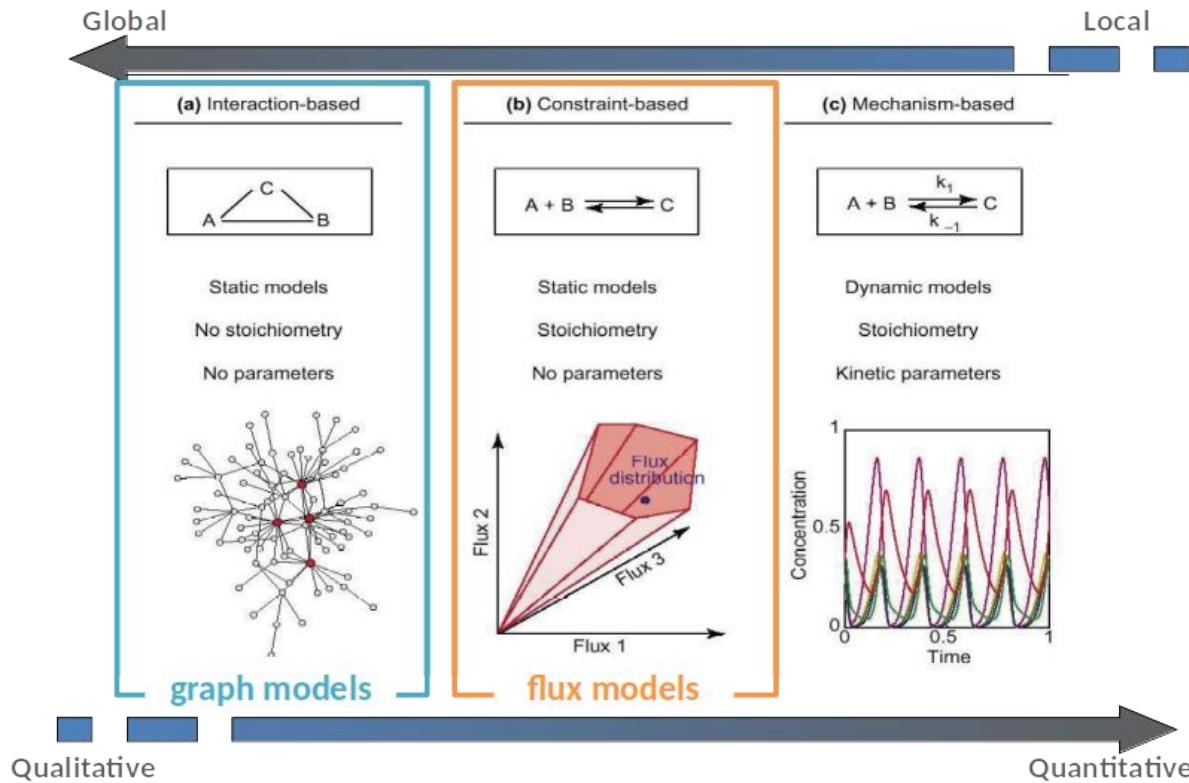
Metabolic networks to metabolic models

The behavior of the whole system cannot be deduced from the analysis of its individual components

Metabolic network: textual description

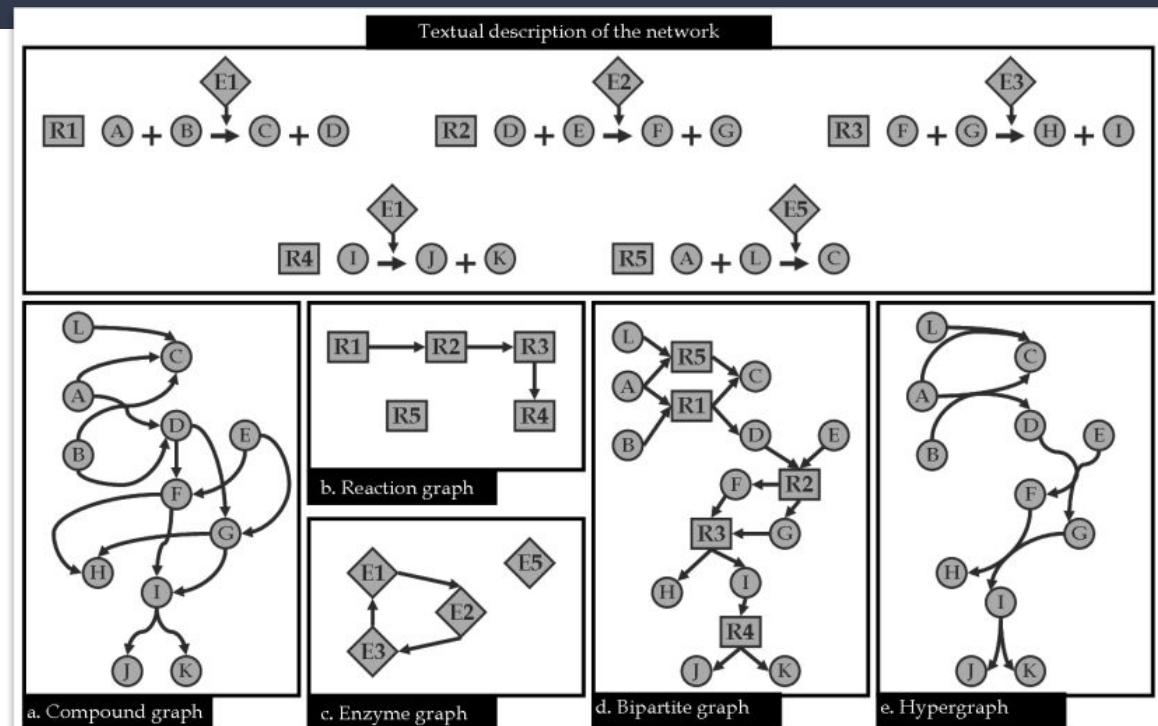


Metabolic models



Graph models

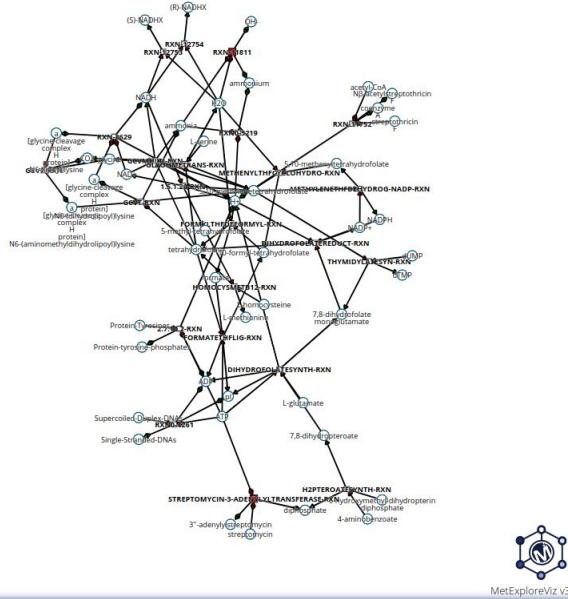
Metabolic graphs are built from the descriptions of the set of reactions that constitute a metabolic network



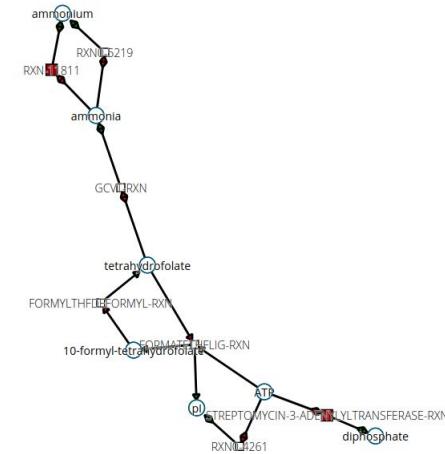
Sub-network extraction

Extract the lightest network connecting the selected links

- Link
- ↔ Reversible link
- Reaction
- Metabolites



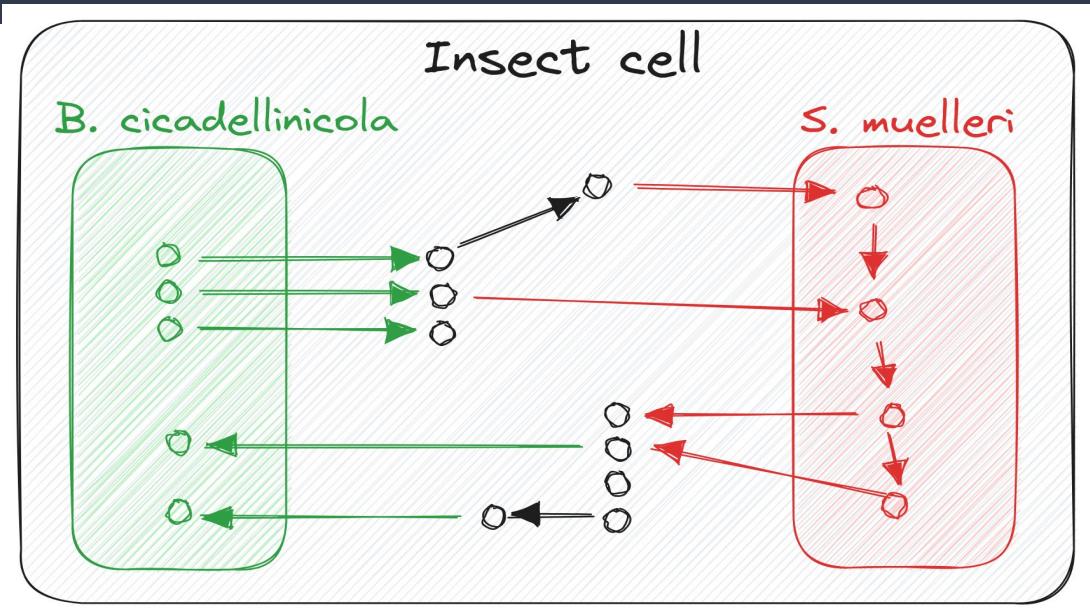
- Link
- ↔ Reversible link
- Reaction
- Metabolites



Graph models to analyse metabolic interactions



Wu D et al. (2006) **Metabolic Complementarity and Genomics of the Dual Bacterial Symbiosis of Sharpshooters.** PLOS Biology 4(6): e188.



Cottret L, Milreu PV, Acuña V, Marchetti-Spaccamela A, Stougie L, Charles H, Sagot MF. **Graph-based analysis of the metabolic exchanges between two co-resident intracellular symbionts, *Baumannia cicadellinicola* and *Sulcia muelleri*, with their insect host, *Homalodisca coagulata*.** PLoS Comput Biol. 2010 Sep 2;6(9):e1000904..

Flux Balance Analysis (FBA)

hypothesis = the time constants characterizing metabolic transients are typically very rapid compared to the time constants of cell growth, so that we consider a steady-state behavior for all system metabolites

for each metabolite i:

$$\frac{dS_i}{dt} = 0 \Leftrightarrow \sum v_{R_{synthesis}} = \sum v_{R_{degradation}}$$

for the network:

$$\frac{dS}{dt} = S \cdot v = 0$$

Mass balance equations

$$\frac{dA}{dt} = -int_1 - int_2 + int_3 + ex_1$$
$$\frac{dB}{dt} = int_1 + int_4 - ex_2$$
$$\frac{dC}{dt} = int_2 - int_3 - int_4 - ex_3$$



Steady state:

$$-int_1 - int_2 + int_3 + ex_1 = 0$$
$$int_1 + int_4 - ex_2 = 0$$
$$int_2 - int_3 - int_4 - ex_3 = 0$$

Matrix form: $S \cdot v = 0$

$$\begin{bmatrix} int_1 \\ int_2 \\ int_3 \\ int_4 \\ ex_1 \\ ex_2 \\ ex_3 \end{bmatrix} = 0$$
$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & -1 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & -1 & -1 & 0 & 0 & -1 \end{bmatrix} \times \begin{bmatrix} int_1 \\ int_2 \\ int_3 \\ int_4 \\ ex_1 \\ ex_2 \\ ex_3 \end{bmatrix} = 0$$

Flux Balance Analysis (FBA)

for each reaction R_j : $v_{j,\min} \leq v_j \leq v_{j,\max}$

in the matrix format:

$$lb \leq v \leq ub$$

avec $lb = [v_{1,\min}; \dots; v_{j,\min}; \dots; v_{n,\min}]$
et $ub = [v_{1,\max}; \dots; v_{j,\max}; \dots; v_{n,\max}]$

how to determine the bounds?

1. by default $lb = -\infty$
 $ub = +\infty$

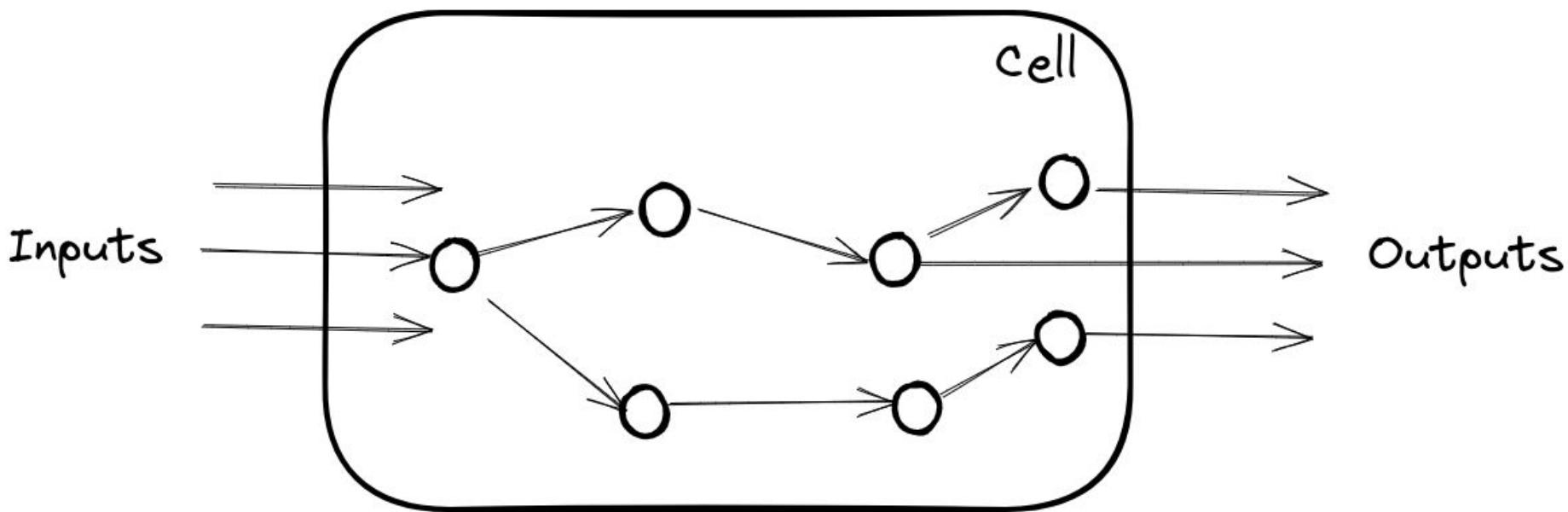
2. possible constraints:

thermodynamic: $0 < v < +\infty$

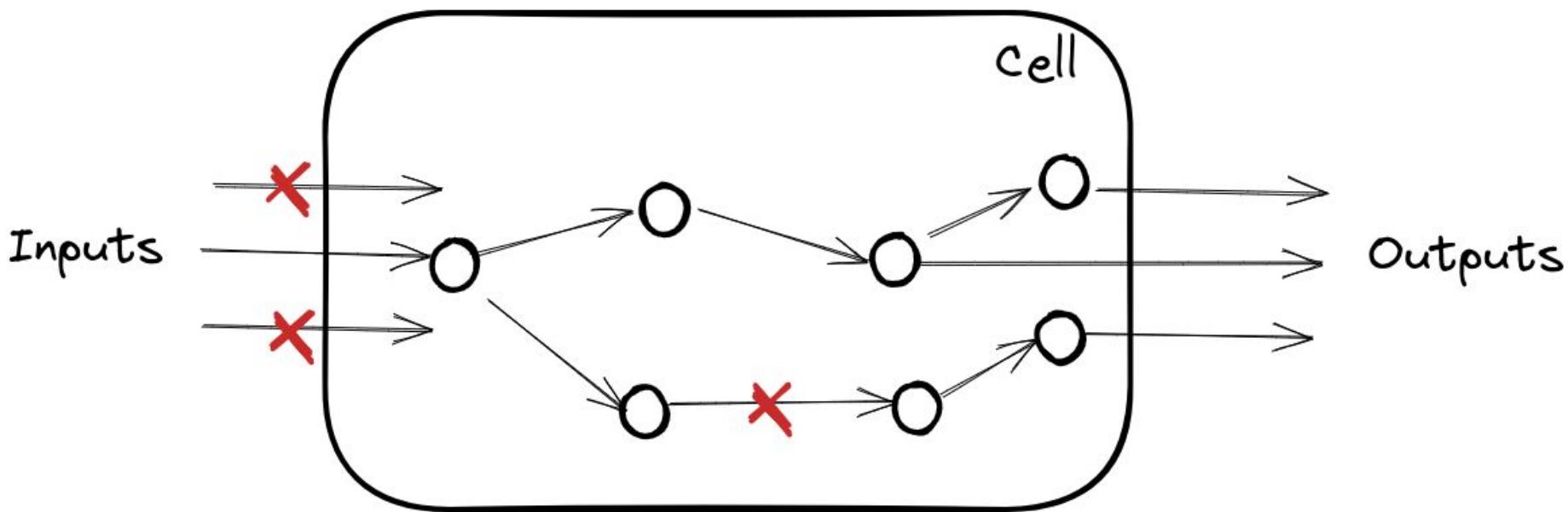
enzymatic capacity: $a < v < b$

for exchange reactions: $v > 0 \leftrightarrow \text{secretion}$
 $v < 0 \leftrightarrow \text{intake}$

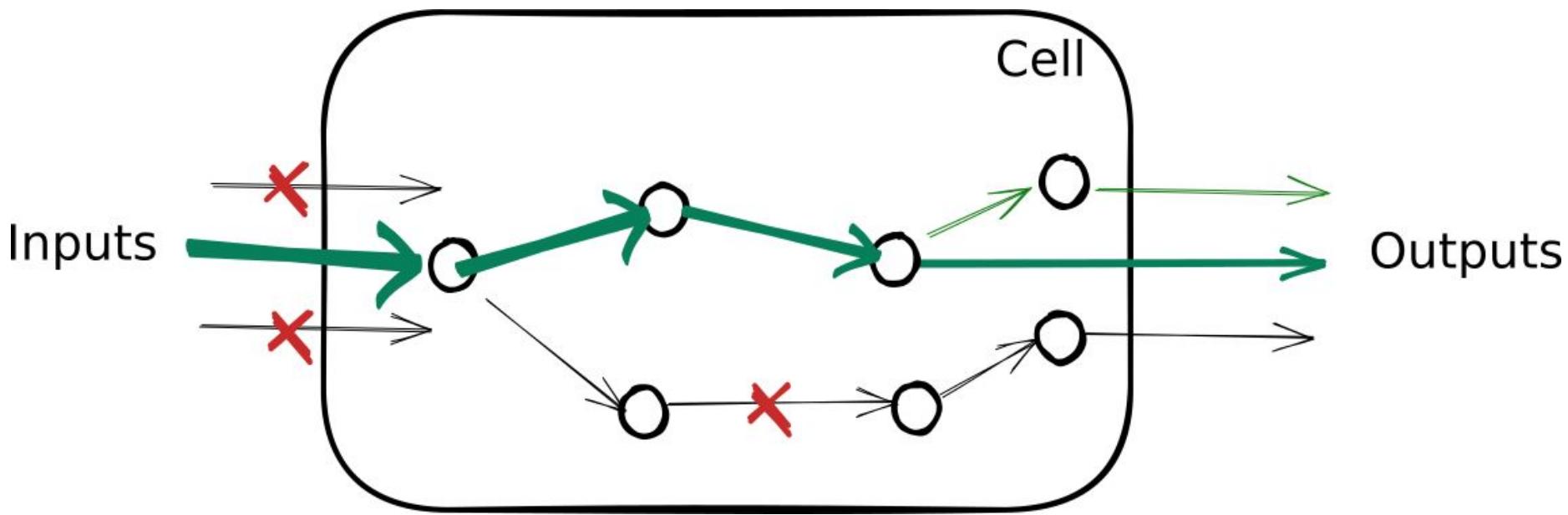
Flux Balance Analysis (FBA)



FBA: environmental and genetic constraints

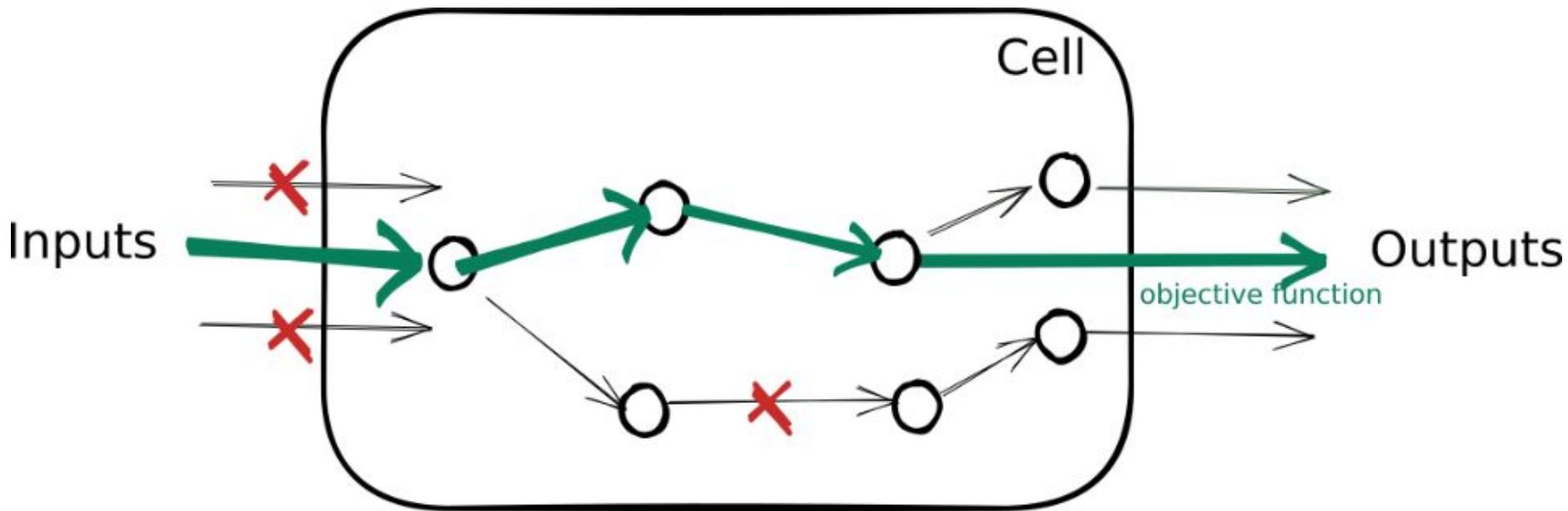


FBA: environmental and genetic constraints



FBA: optimise an objective function

Orth, J., Thiele, I. & Palsson, B. What is flux balance analysis?. *Nat Biotechnol* 28, 245–248 (2010).



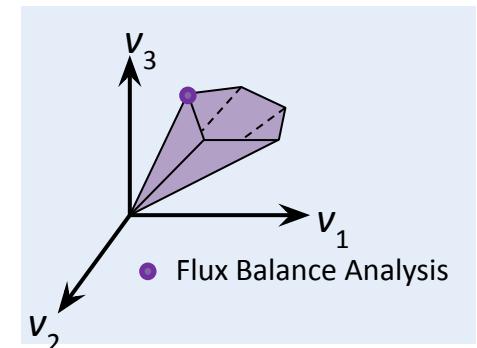
A linear programming optimization problem

Aim = finding one particular solution in the entire solution space (optimal solution under some conditions)

Concept = the cell functions in an optimal metabolic state (e.g. optimal growth under given conditions)

→ Output of FBA = particular flux distribution which maximizes or minimizes an objective function

$$\left\{ \begin{array}{l} \text{max: } Z \\ \text{subject to:} \\ \quad S \cdot v = 0 \\ \quad l_b \leq v \leq u_b \end{array} \right.$$



Flux Balance Analysis

- Optimize biomass or production of metabolites of interest
- Analysis of environmental, enzymatic or genetic perturbations (e: *in silico* gene deletions)
- Generate sub-networks from transcriptomics data
- Just one of many solutions

Use case with MetExplore: mRNA mapping for BRCA context

MetExplore

MetExplore Computational infrastructure for metabolic network analysis

Funding: ANR MetaboHub, H2020 Phenomenal

- Long lasting project established in 2009

- 842 registered users, >540 persons trained, >20 000 visits since 2009

- > 1300 networks

- Publications:

Cottret et al (2018). Nucleic Acids Research

Chazalviel et al (2017). Bioinformatics

→>140 citations

W49-W50 Nucleic Acids Research, 2018, Vol. 38, Web Server issue doi:10.1093/nar/gky302

Published online 3 May 2018

MetExplore: a web server to link metabolomic experiments and genome-scale metabolic networks

Ludovic Cottret^{1,*},
Hubert Charles^{2,*}

Nucleic Acids Research, 2018, Vol. 46, Web Server issue W49-W50
doi:10.1093/nar/gky302

MetExplore: collaborative edition and exploration of metabolic networks

Ludovic Cottret^{1,*}, Clément Frainay², Maxime Chazalviel^{2,3}, Floréal Cabanettes¹, Yoann Gloaguen^{4,5,6}, Etienne Camenen², Benjamin Merlet¹, Stéphanie Heuz^{7,8,9}, Jean-Charles Portais^{7,8,9}, Nathalie Poupin², Florence Vinson¹ and Fabien Jourdan^{7,2}

Systems biology

MetExploreViz: web component for interactive metabolic network visualization

Maxime Chazalviel^{1,2}, Clément Frainay¹, Nathalie Poupin¹, Florence Vinson¹, Benjamin Merlet¹, Yoann Gloaguen², Ludovic Cottret⁴ and Fabien Jourdan^{1,*}



- Involved in several national and EU grants
- 1 industrial partner (MedDay pharma)



Website: <http://www.metexplore.fr/>



- Database of metabolic networks
- Collaborative annotation of metabolic networks
- Import of omics data
- Visualization of metabolic networks
- Flux Balance Analysis
- Sub-network extraction (graph based computations)



Ludovic Cottret
IR INRAE



Florence Vinson
IE INRAE



Marion Liotier
CDD IE MetaboHub

Select a BioSource

BioSource:

metabolic network built for a strain, a cell line or a specific condition

Recon2.2 Swainston 2016 - Reconstruction of human metabolic network

MetExplore v2.32.12

About Omics Toolbox Flux Import Export Login

User Profile Network Data Network Curation Network Viz

BioSources Compartments (10/10) Pathways (99/99) Reactions (7785/7785) Metabolites (6047/6047) Enzymatic Complexes (1815/1815) Gene Products (1675/1675) Genes (1675/1675)

You can change the grouping option here: Group Table Group by:

	ID	Name	Source Database	Database Type	Nb Reactions	Nb Metabolites	Nb Genes
1	Harpegnathos saltator						
2	Helianthus annuus						
3	Helicobacter pylori						
4	Heliconius melpomene						
5	Homo sapiens						
159	1...	Recon 2.02 Human metabolism global reconstruction (Recon 2) - model - ...	Publication	Others (SBML,...)	7440	5063	2191
160	1...	Hsap	BioCyc	BioCyc	2527	2701	3583
161	1...	Recon 1 Homo_sapiens	Publication	Others (SBML,...)	3742	3188	1905
162	1...	Homo sapiens (human) KEGG Genes Database	KEGG Map	KEGG	1869	1560	1417
163	1...	Recon 2.03, enriched with additional database refs, without compartment...	MetExplore	Others (SBML,...)	4210	2592	1893
164	1...	HepatocyteNet Gille2010	Publication	Others (SBML,...)	2539	1420	0
165	1...	Swainston2016 - Reconstruction of human metabolic network (Recon 2.2)	Publication	Others (SBML,...)	7785	6047	1675
166	1...	Recon 2.04 - Human metabolic global reconstruction	VMH	Others (SBML,...)	7440	5063	2140
167	1...	iHsa_Ratcom1	Publication	Others (SBML,...)	8264	5620	2315
168	1...	Homo sapiens (human) KEGG Genes Database	KEGG Map	KEGG	1931	1572	1455
169	1...	Recon 2.03 (initial - VMH)	VMH	Others (SBML,...)	7440	5063	2191
170	1...	Recon 3D	VMH	SBML	13543	8399	3697
171	1...	Recon3D Flat	MetExplore	SBML	5389	4095	2990
172	1...	Human Metabolic Reaction HMR2.00 (xlsx)	HMA	Others (SBML,...)	8181	6006	3765
173	1...	Human1 (HumanGEM)	Publication	SBML	13097	10073	3628
174	1...	Homo sapiens (human) KEGG Genes Database	KEGG Map	KEGG	2067	1618	1456
175	1...	Human_1.7 (HumanGEM)	SBML	SBML	13082	8378	3625
176	1...	ihsan1.10	humanGEM github	SBML	13078	8370	3625
177		Hordeum vulgare					
178		Hydra vulgaris					
179		Ixodes scapularis					
180		Klebsiella pneumoniae					
181		Lactobacillus casei					

Selected BioSource

Public: Homo sapiens (Strain: Global) (Source: Publication, Version: Recon2.2)

Private: -- Select private BioSource --

Homo sapiens (Strain: Global) (Source: Publication, Version: Recon2.2)

copy this BioSource

Compart	Path	Rxn	Met	E_Cpx	G_Prod	Genes
10	99	7785	6047	1815	1675	1675

BioSource Data

MetExplore Id: 4311

Name: Swainston2016 - Reconstruction of human metabolic network (Recon 2.2)

Organism: Homo sapiens

Tissue: global

Cell Type:

Strain: Global

Source Database: Publication

URL:

Id in Database: MODEL1603150001

Version: Recon2.2

Database type: Others (SBML,...)

Publication

Swainston N et al., 2016

Cart

Jobs

Filters

Matching identifiers

Convert geneSymbol to HGNC, Ensembl, ...

Many online tools to convert:

<https://www.genenames.org/tools/multi-symbol-checker/>

MetExplore v2.32.12

About Omics Toolbox Flux Import Export Login

User Profile Network Data Network Curation Network Viz

BioSources Compartments (10/10) Pathways (99/99) Reactions (7785/7785) Metabolites (6047/6047) Enzymatic Complexes (1815/1815) Gene Products (1675/1675) Genes (1675/1675)

Add Edit Delete Curation Votes Load Aliases

Name	Identifier
exact sub-string search	exact sub-string search
1 HGNC:10006	HGNC:10006
2 HGNC:1027	HGNC:1027
3 HGNC:10293	HGNC:10293
4 HGNC:10297	HGNC:10297
5 HGNC:10451	HGNC:10451
6 HGNC:10452	HGNC:10452
7 HGNC:1047	HGNC:1047
	HGNC:1048
	HGNC:10536
	HGNC:10540
	HGNC:10545
	HGNC:10547
	HGNC:10571
	HGNC:10606
	HGNC:1062
	HGNC:1063
	HGNC:10680
	HGNC:10681
	HGNC:10682
	HGNC:10683
	HGNC:10691
	HGNC:10761
22 HGNC:10701	
23 HGNC:108	HGNC:108
24 HGNC:10817	HGNC:10817
25 HGNC:10818	HGNC:10818
26 HGNC:10850	HGNC:10850
27 HGNC:10852	HGNC:10852
28 HGNC:10856	HGNC:10856
29 HGNC:10860	HGNC:10860
30 HGNC:10862	HGNC:10862
31 HGNC:10863	HGNC:10863

Mapping genes

**Missing data: few
explanations**

- Identifiers
- Incomplete network
- **Not metabolism
genes**

Screenshot of the MetExplore v2.32.12 interface, specifically the "Mapping" tab.

The interface includes a top navigation bar with links for About, Omics, Toolbox, Flux, Import, Export, and Login. Below the navigation is a sub-navigation bar with tabs for User Profile, Network Data, Network Curation, Network Viz, and Mapping (which is active).

On the left, there is a "Demo" button and a file upload section with fields for "Upload file (.csv .txt)" and "separator: tab". There are also checkboxes for "Consider first row as header of columns" and "Perform one separate mapping for each column".

The main area features a "Copy/Paste in grid" table. The table has columns for "Identifier" and "Feature". The data is as follows:

	Identifier	Feature
1	false	HGNC:16488
2	false	HGNC:30932
3	false	HGNC:1349
4	false	HGNC:5411
5	false	HGNC:5397
6	false	HGNC:5414
7	false	HGNC:30908
8	false	HGNC:5409

Below the table, there is a "Propagate:" dropdown menu set to "without conditions values".

At the bottom, there are buttons for "Map" and "Save Mapping in File".

At the very bottom, status information is displayed: "Mapping Nb Data: 2050 Nb Data In Network: 223 Nb Mapped: 221".

Mapping genes

Mapping data appear on grids

BioSources		Compartments (10/10)		Pathways (99/99)		Reactions (7785/7785)		Metabolites (6047/6047)		Enzymatic Complexes (1815/1815)		Gene Products (1675/1675)		Genes (1675/1675)	
		Add	Edit	Delete	Curation Votes	Load Aliases									
Name					Identifier					Mapping					
exact sub-string search					exact sub-string search					identified ↓					
1	HGNC:1027				HGNC:1027					true			3		
2	HGNC:10571				HGNC:10571					true			5		
3	HGNC:1063				HGNC:1063					true			8		
4	HGNC:10860				HGNC:10860					true			2		
5	HGNC:10862				HGNC:10862					true			4		
6	HGNC:10872				HGNC:10872					true			2		
7	HGNC:10909				HGNC:10909					true			3		
8	HGNC:10911				HGNC:10911					true			4		
9	HGNC:10922				HGNC:10922					true			8		
10	HGNC:10923				HGNC:10923					true			5		
11	HGNC:10924				HGNC:10924					true			2		
12	HGNC:10937				HGNC:10937					true			9		
13	HGNC:10938				HGNC:10938					true			8		
14	HGNC:10941				HGNC:10941					true			2		
15	HGNC:10942				HGNC:10942					true			8		
16	HGNC:10952				HGNC:10952					true			2		
17	HGNC:10962				HGNC:10962					true			2		
18	HGNC:10969				HGNC:10969					true			8		
19	HGNC:11005				HGNC:11005					true			9		
20	HGNC:11007				HGNC:11007					true			7		
21	HGNC:11023				HGNC:11023					true			4		
22	HGNC:11033				HGNC:11033					true			4		
23	HGNC:11041				HGNC:11041					true			8		
24	HGNC:11055				HGNC:11055					true			8		
25	HGNC:11056				HGNC:11056					true			5		
26	HGNC:11057				HGNC:11057					true			9		
27	HGNC:11063				HGNC:11063					true			9		
28	HGNC:11065				HGNC:11065					true			2		
29	HGNC:11066				HGNC:11066					true			8		
30	HGNC:11177				HGNC:11177					true			2		

FBA: optimize biomass reactions

Hypothesis: cancer cell seeks to facilitate its proliferation by increasing its production of biomass

- Optimize biomass reaction for Flux Balance Analysis

The screenshot shows the 'Flux Balance Analysis' tab selected in a software interface. The interface includes tabs for User Profile, Network Data, Network Curation, Network Viz, and Flux Balance Analysis. The main area contains several input fields and dropdown menus for setting parameters:

- Description:** Computes the optimal value of an objective reaction.
- Analysis title:** Flux Balance Analysis.
- Standard Parameters:**
 - objectiveReactions:** R_biomass_reaction. A button labeled "report reaction table selection" is visible.
 - objectiveSense:** MAX (radio button selected).
 - secondObjectiveReactions:** An empty dropdown menu. A button labeled "report reaction table selection" is visible.
 - secondObjectiveSense:** MAX (radio button selected).
 - libertyPercentage:** 0.
 - ko_genes:** An empty dropdown menu. A button labeled "report gene table selection" is visible.
 - ko_reactions:** An empty dropdown menu. A button labeled "report reaction table selection" is visible.
- Launch:** A blue button at the bottom left of the parameter area.

Filters

Propagation of the filters

Interlinked grids: filtering one affects the content of the other ones

BioSources	Compartments (10/10)	Pathways (99/99)	Reactions (7785/7785)	Metabolites (6047/6047)	Enzymatic Complexes (1815/1815)	Gene Products (1675/1675)	Genes (1675/1675)
Add Edit Delete Curation Votes Load Aliases							
	Name		Identifier		Mapping	X	
	exact sub-string search		exact sub-string search		identified ↓	condition0	
1	HGNC-1027		HGNC-1027		true	3	
2	HGNC-10571		HGNC-10571		true	5	
3	HGNC-1063		HGNC-1063		true	8	
4	HGNC-10860		HGNC-10860		true	2	
5	HGNC-10862		HGNC-10862		true	4	
6	HGNC-10872		HGNC-10872		true	2	
7	HGNC-10909		HGNC-10909		true	3	
8	HGNC-10911		HGNC-10911		true	4	
9	HGNC-10922		HGNC-10922		true	8	
10	HGNC-10923		HGNC-10923		true	5	
11	HGNC-10924		HGNC-10924		true	2	
12	HGNC-10937		HGNC-10937		true	9	
13	HGNC-10938		HGNC-10938		true	8	
14	HGNC-10941		HGNC-10941		true	2	
15	HGNC-10942		HGNC-10942		true	8	
16	HGNC-10952		HGNC-10952		true	2	
17	HGNC-10962		HGNC-10962		true	2	
18	HGNC-10969		HGNC-10969		true	8	
19	HGNC-11005		HGNC-11005		true	9	
20	HGNC-11007		HGNC-11007		true	7	
21	HGNC-11023		HGNC-11023		true	4	
22	HGNC-11033		HGNC-11033		true	4	
23	HGNC-11041		HGNC-11041		true	8	
24	HGNC-11055		HGNC-11055		true	8	
25	HGNC-11056		HGNC-11056		true	5	
26	HGNC-11057		HGNC-11057		true	9	
27	HGNC-11063		HGNC-11063		true	9	
28	HGNC-11065		HGNC-11065		true	2	
29	HGNC-11066		HGNC-11066		true	8	

Filters: genes mapped

BioSources Compartments (9/10) Pathways (78/99) Reactions (1269/7785) Metabolites (1629/6047) Enzymatic Complexes (263/1815) Gene Products (221/1675) Genes (221/1675)			
<input type="button" value="Add"/> <input type="button" value="Edit"/> <input type="button" value="Delete"/> <input type="button" value="Curation Votes"/> <input type="button" value="Load Aliases"/>			
Name	Identifier	Mapping	
exact sub-string search	exact sub-string search	identified ↓	condition0
1 HGNC:1027	HGNC:1027	true	3
2 HGNC:10571	HGNC:10571	true	5
3 HGNC:1063	HGNC:1063	true	8
4 HGNC:10860	HGNC:10860	true	2
5 HGNC:10862	HGNC:10862	true	4
6 HGNC:10872	HGNC:10872	true	2
7 HGNC:10909	HGNC:10909	true	3
8 HGNC:10911	HGNC:10911	true	4
9 HGNC:10922	HGNC:10922	true	8
10 HGNC:10923	HGNC:10923	true	5
11 HGNC:10924	HGNC:10924	true	2
12 HGNC:10937	HGNC:10937	true	9
13 HGNC:10938	HGNC:10938	true	8
14 HGNC:10941	HGNC:10941	true	2
15 HGNC:10942	HGNC:10942	true	8
16 HGNC:10952	HGNC:10952	true	2
17 HGNC:10962	HGNC:10962	true	2
18 HGNC:10969	HGNC:10969	true	8
19 HGNC:11005	HGNC:11005	true	9
20 HGNC:11007	HGNC:11007	true	7
21 HGNC:11023	HGNC:11023	true	4
22 HGNC:11033	HGNC:11033	true	4
23 HGNC:11041	HGNC:11041	true	8
24 HGNC:11055	HGNC:11055	true	8
25 HGNC:11056	HGNC:11056	true	5
26 HGNC:11057	HGNC:11057	true	9
27 HGNC:11063	HGNC:11063	true	9
28 HGNC:11065	HGNC:11065	true	2
29 HGNC:11066	HGNC:11066	true	8
30 HGNC:11177	HGNC:11177	true	2

Filters: genes mapped

Interlinked grids: filtering one affects the content of the other ones

- Update data on grids

Ordering data on genes grid by condition (subModules)

- **Missing group 1 (black color)**

BioSources Compartments (9/10) Pathways (78/99) Reactions (1269/7785) Metabolites (1629/6047) Enzymatic Complexes (263/1815) Gene Products (221/1675) Genes (221/1675)			
<input type="button" value="Add"/> <input type="button" value="Edit"/> <input type="button" value="Delete"/> <input type="button" value="Curation Votes"/> <input type="button" value="Load Aliases"/>			
Name	Identifier	Mapping	
exact sub-string search	exact sub-string search	identified ↓	condition0
1 HGNC:1027	HGNC:1027	true	3
2 HGNC:10571	HGNC:10571	true	5
3 HGNC:1063	HGNC:1063	true	8
4 HGNC:10860	HGNC:10860	true	2
5 HGNC:10862	HGNC:10862	true	4
6 HGNC:10872	HGNC:10872	true	2
7 HGNC:10909	HGNC:10909	true	3
8 HGNC:10911	HGNC:10911	true	4
9 HGNC:10922	HGNC:10922	true	8
10 HGNC:10923	HGNC:10923	true	5
11 HGNC:10924	HGNC:10924	true	2
12 HGNC:10937	HGNC:10937	true	9
13 HGNC:10938	HGNC:10938	true	8
14 HGNC:10941	HGNC:10941	true	2
15 HGNC:10942	HGNC:10942	true	8
16 HGNC:10952	HGNC:10952	true	2
17 HGNC:10962	HGNC:10962	true	2
18 HGNC:10969	HGNC:10969	true	8
19 HGNC:11005	HGNC:11005	true	9
20 HGNC:11007	HGNC:11007	true	7
21 HGNC:11023	HGNC:11023	true	4
22 HGNC:11033	HGNC:11033	true	4
23 HGNC:11041	HGNC:11041	true	8
24 HGNC:11055	HGNC:11055	true	8
25 HGNC:11056	HGNC:11056	true	5
26 HGNC:11057	HGNC:11057	true	9
27 HGNC:11063	HGNC:11063	true	9
28 HGNC:11065	HGNC:11065	true	2
29 HGNC:11066	HGNC:11066	true	8
30 HGNC:11177	HGNC:11177	true	2

Pathways enrichment

On mapping: automatique
pathways enrichment with p-value
and corrected p-value

With correction, 4 pathways have
been identified:

- Fatty acid oxidation
- Fatty acid synthesis
- Eicosanoid metabolism
- Glutamate metabolism

Filters data on this 4 pathways

BioSources		Compartments (9/10)		Pathways (78/99)		Reactions (1269/7785)		Metabolites (1629/6047)		Enzymatic Complexes (263/1815)		Gene Products (221/1675)		Genes (221/1675)		
		Add	Edit	Delete	Curation Statistics	Votes										
	Name	Identifier		Nb Reactions	% Reactions with Enz.	Coverage	Nb of Mapped	p-value	Bonferroni corre	BH-corrected p-						
1	Fatty acid oxidation	Fatty acid oxidation		809	78 %	24.14	21	3.13e-3	(2.44e-1)	(1.25e-1)						
2	Fatty acid synthesis	Fatty acid synthesis		118	60 %	41.18	7	3.82e-3	(2.98e-1)	(1.25e-1)						
3	Eicosanoid metabolism	Eicosanoid metabolism		252	62 %	24.66	18	4.83e-3	(3.76e-1)	(1.25e-1)						
4	Glutamate metabolism	Glutamate metabolism		15	93 %	35	7	1.07e-2	(8.37e-1)	(2.09e-1)						
5	Transport, extracellular	Transport, extracellular		1472	79 %	14.05	34	3.68e-1	(1.00e+0)	(7.96e-1)						
6	Nucleotide interconversion	Nucleotide interconversion		177	93 %	12.93	15	5.79e-1	(1.00e+0)	(8.86e-1)						
7	Inositol phosphate metabolism	Inositol phosphate metabolism		64	65 %	18.33	11	1.57e-1	(1.00e+0)	(6.13e-1)						
8	Glycolysis/gluconeogenesis	Glycolysis/gluconeogenesis		40	100 %	12.99	10	5.75e-1	(1.00e+0)	(8.86e-1)						
9	Valine, leucine, and isoleucine metabolism	Valine, leucine, and isoleucine m...		41	85 %	27.03	10	1.77e-2	(1.00e+0)	(2.76e-1)						
10	Sphingolipid metabolism	Sphingolipid metabolism		83	91 %	18	9	2.05e-1	(1.00e+0)	(6.38e-1)						
11	Pyruvate metabolism	Pyruvate metabolism		30	83 %	22.5	9	7.06e-2	(1.00e+0)	(4.99e-1)						
12	O-glycan synthesis	O-glycan synthesis		15	73 %	30.43	7	2.40e-2	(1.00e+0)	(2.67e-1)						
13	Miscellaneous	Miscellaneous		86	69 %	9.09	7	9.02e-1	(1.00e+0)	(1.05e+0)						
14	Cholesterol metabolism	Cholesterol metabolism		57	82 %	24.14	7	7.68e-2	(1.00e+0)	(4.99e-1)						
15	Arginine and Proline Metabolism	Arginine and Proline Metabolism		39	74 %	22.58	7	1.03e-1	(1.00e+0)	(5.07e-1)						
16	Pyrimidine catabolism	Pyrimidine catabolism		35	82 %	25	7	6.53e-2	(1.00e+0)	(4.99e-1)						
17	Glyoxylate and dicarboxylate metabolism	Glyoxylate and dicarboxylate met...		15	73 %	23.33	7	8.94e-2	(1.00e+0)	(5.37e-1)						
18	Triacylglycerol synthesis	Triacylglycerol synthesis		13	100 %	21.43	6	1.54e-1	(1.00e+0)	(6.13e-1)						
19	Glycerophospholipid metabolism	Glycerophospholipid metabolism		66	77 %	8.45	6	9.24e-1	(1.00e+0)	(1.05e+0)						
20	Tryptophan metabolism	Tryptophan metabolism		68	70 %	11.54	6	7.03e-1	(1.00e+0)	(9.79e-1)						
21	Bile acid synthesis	Bile acid synthesis		125	75 %	13.95	6	5.10e-1	(1.00e+0)	(8.75e-1)						
22	Fructose and mannose metabolism	Fructose and mannose metaboli...		25	80 %	20	6	1.95e-1	(1.00e+0)	(6.60e-1)						
23	Tyrosine metabolism	Tyrosine metabolism		117	70 %	8.2	5	9.22e-1	(1.00e+0)	(1.05e+0)						
24	Vitamin C metabolism	Vitamin C metabolism		16	25 %	35.71	5	2.79e-2	(1.00e+0)	(2.73e-1)						
25	Propanoate metabolism	Propanoate metabolism		13	61 %	22.73	5	1.54e-1	(1.00e+0)	(6.13e-1)						
26	Histidine metabolism	Histidine metabolism		16	68 %	21.74	5	1.77e-1	(1.00e+0)	(6.27e-1)						
27	Urea cycle	Urea cycle		68	63 %	20	5	2.26e-1	(1.00e+0)	(6.63e-1)						
28	N-glycan synthesis	N-glycan synthesis		81	40 %	16.67	4	3.92e-1	(1.00e+0)	(7.85e-1)						
29	Purine catabolism	Purine catabolism		36	77 %	14.29	4	5.16e-1	(1.00e+0)	(8.75e-1)						
30	Starch and sucrose metabolism	Starch and sucrose metabolism		32	84 %	16	4	4.24e-1	(1.00e+0)	(8.03e-1)						

Data exploration

By checking scientific literature, we can find some articles that confirm the results found:

- Monaco ME. Fatty acid metabolism in breast cancer subtypes. *Oncotarget*. 2017

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5438746/#:~:text=Evidence%20indicates%20that%20proteins%20involved,invasion%20of%20breast%20cancer%20cells.>

- Fazzari, J., Lin, H., Murphy, C. et al. Inhibitors of glutamate release from breast cancer cells; new targets for cancer-induced bone-pain. *Sci Rep.* 2015

<https://www.nature.com/articles/srep08380#:~:text=Breast%20cancer%20cells%20secrete%20high,advanced%2Dstage%20breast%20cancer%20patients.>

- Wang D, Dubois RN. Eicosanoids and cancer. *Nat Rev Cancer*. 2010

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898136/>

- Yi H, Talmon G, Wang J. Glutamate in cancers: from metabolism to signaling. *J Biomed Res*. 2019

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7386414/>

Filters: FBA result

Only reactions with a non-zero flux value are kept

65 reactions of interest remain

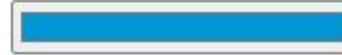
Visualise this sub-network

BioSources		Compartments (5/10)		Pathways (4/99)		Reactions (65/7785)		Metabolites (160/6047)		Enzymatic Complexes (23/1815)		Gene Products (18/1675)		Genes (221/1675)	
		Add	Edit	Delete	Save	Multiple affectation	Curation Statistics	Curation Votes	Equations	Load Aliases					
		Name	Identifier	EC.	GPR										
		exact sub-string search	exact sub-string sear	exact s											
1	1	EC:1.1.1.35	R_r1477	23.1.86	(HGNC:4799 and HGNC:3247 and H...	✓	-Infinity	Infinity	25	1	-39446.6236				
2	1	(3R)-3-Hydroxybutanoyl-[acyl-carri...	R_r0693	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
3	1	(3R)-3-Hydroxybutanoyl-[acyl-carri...	R_r0681	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
4	1	(3R)-3-Hydroxybutanoyl-[acyl-carri...	R_r0770	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
5	1	(3R)-3-Hydroxybutanoyl-[acyl-carri...	R_r0762	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
6	1	(3R)-3-Hydroxybutanoyl-[acyl-carri...	R_r0695	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
7	1	Acetyl-CoA ACP transacylase	R_ACOATA	23.1.38	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
8	1	Acyl-[acyl-carrier-protein]:malonyl-...	R_r0678	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
9	1	butyryl-[acyl-carrier protein]:malon...	R_r0760	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
10	1	Decanoyl-[acyl-carrier protein]:mal...	R_r0768	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
11	1	hexanoyl-[acyl-carrier protein]:malo...	R_r0764	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
12	1	Octanoyl-[acyl-carrier protein]:malo...	R_r0766	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-39999.6				
13	1	fatty-acid--CoA ligase	R_FACOAL1831	6.2.1.3	(HGNC:24174) or (HGNC:16526) or (...)	✓	-Infinity	Infinity	50	3	-53104.4779				
14	1	Hexadecanoyl-[acyl-carrier protein]...	R_r0773	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-55372.1728				
15	1	Succinate-semialdehyde:NAD+ oxid...	R_r0178	12.1.24	(HGNC:408)	✓	-Infinity	Infinity	100	1	-65146.914				
16	1	RE3250	R_RE3250X	1.1.1.35	(HGNC:5213) or (HGNC:3247)	✓	-Infinity	Infinity	50	1	-81619.7117				
17	1	(3R)-3-Hydroxypalmitoyl-[acyl-carri...	R_r0696	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-99999.0				
18	1	4-Aminobutyraldehyde:NAD+ oido...	R_r0464	12.1.3	(HGNC:412) or (HGNC:407) or (HG...	✓	-Infinity	Infinity	40	2	-99999.0				
19	1	camitine dimethyl nonanoyl transfe...	R_CSNAT2x	23.1.7	(HGNC:2342) or (HGNC:2366)	✓	-Infinity	Infinity	100	2	-99999.0				
20	1	camitine O-acetyltransferase	R_CSNATr	23.1.7	(HGNC:2342)	✓	-Infinity	Infinity	100	1	-99999.0				
21	1	EC:6.2.1.3	R_r1487	6.2.1.3	(HGNC:24174) or (HGNC:16526) or (...)	✓	-Infinity	Infinity	42.86	3	-99999.0				
22	1	fatty-acid--CoA ligase	R_FACOAL1821	6.2.1.3	(HGNC:24174) or (HGNC:3571) or (...)	✓	-Infinity	Infinity	50	2	-99999.0				
23	1	fatty-acid--CoA ligase	R_FACOAL1812	6.2.1.3	(HGNC:3569)	✓	-Infinity	Infinity	100	1	-99999.0				
24	1	Malonyl-CoA-ACP transacylase	R_MCOATA	23.1.85	(HGNC:3594)	✓	-Infinity	Infinity	100	1	-99999.0				
25	1	production of octanoylcarnitine	R_C80CPT1	NA	(HGNC:18540) or (HGNC:2328) or (...)	✓	-Infinity	Infinity	66.67	2	-99999.0				
26	1	RE3074	R_RE3074X	6.2.1.3	(HGNC:16526) or (HGNC:3571) or (...)	✓	-Infinity	Infinity	50	3	-99999.0				
27	1	transport of Octadecenoyl-CoA into ...	R_OCTDECCPT1	NA	(HGNC:18540) or (HGNC:2328) or (...)	✓	-Infinity	Infinity	66.67	2	-99999.0				
28	1	fatty acid beta oxidation(C22:1->C...	R_FAOXC22C201x	NA	(HGNC:82 and HGNC:3247 and HG...	□	0	Infinity	25	1	14953.7117				
29	1	fatty acid beta oxidation(C24:1->C...	R_FAOXC24C221x	NA	(HGNC:119 and HGNC:10606 and H...	□	0	Infinity	25	1	14953.7117				
30	1	fatty acid beta oxidation(C20:1->C...	R_FAOXC20C181x	NA	(HGNC:82 and HGNC:3247 and HG...	□	0	Infinity	25	1	14953.7117				

Visualisation

Compartments:

cytoplasm :



endoplasmic reticulum :



mitochondrion :



peroxisome :



Pathways:

Eicosanoid metabolism :



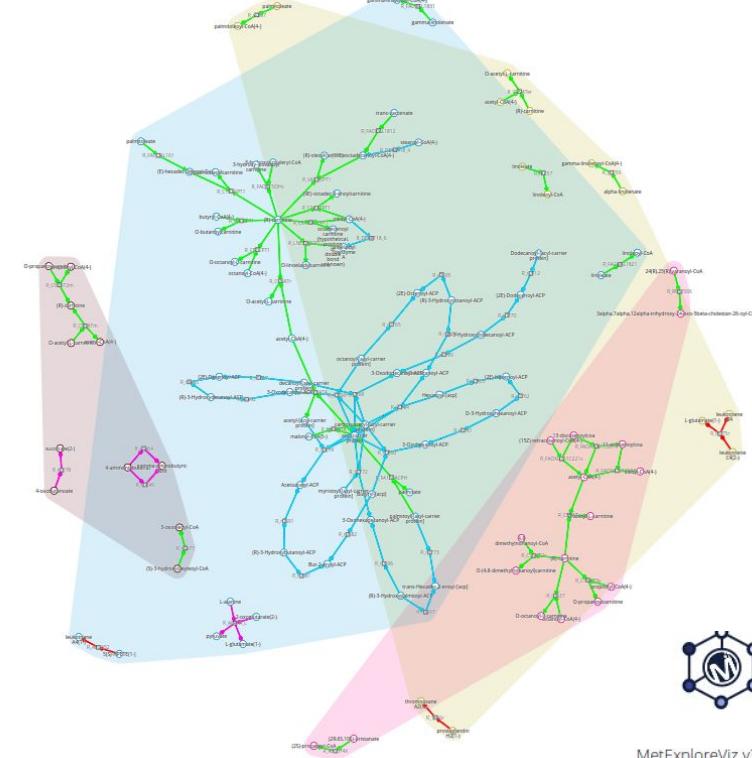
Fatty acid oxidation :



Fatty acid synthesis :



Glutamate metabolism :



Hypothesis

- We have succeeded in highlighting the link between genes and four pathways potentially involved in the development of cancer
- By optimising biomass production, we have shown that the flux that pass through these four pathways
- We can therefore identify a sub-network of interest for the study of breast cancer development, and consequently, a list of metabolites to monitor

To go further with MetExplore

Project creation and collaboration

MetExplore allows users, after login, to create a project and add some collaborators.

On this project you have few possibilities like:

- Import your own network with SBML file, from KEGG DB or MetExplore XML file
- Cure your networks (add, edit or delete data)
- Manage your project (TODO list, comments, history, etc...)

The screenshot shows the MetExplore software interface. At the top, there's a navigation bar with tabs for User Profile, Project Details, Network Data, Network Curation, and Network Viz. The Project Details tab is active, showing a project titled "Projet A-V Splanchnic Postprandial" created on "2018-12-22". Below the navigation bar is a "TODO list" table with columns for Description, Project, User, Limit date, Status, and Priority. The table is currently empty. To the right of the table is a detailed sidebar for "Selected BioSource". The sidebar includes sections for "Public" (with a dropdown menu), "Private" (with a dropdown menu), and "Project" (which is currently selected, showing "Homo sapiens (Strain: Liver) [Source: Gille et al., + modifs NP, Version: HepatoNet1_10r1]"). It also contains sections for "BioSources", "Comments", "History", "Description", and "Users". Under "BioSources", there's a table with columns: Id, Name, Organism, Strain, Source Database, Database Type, and Publication. The table lists five entries, all of which are "HepatoNet1 with EXNrN & AdDR" and "Homo sapiens" with "Liver" as the strain. The "Database type" column shows "SBML" and the "Publication" column shows "Gille et al., 2018". The sidebar also includes sections for "MetExplore Data", "Organism", "Tissue", "Cell Type", "Strain", "Source Database", "URL", "Id in Database", "Version", "Database type", "Publication", "Cart", "Jobs", and "Filters".

Data export

MetExplore allows users to export their data on differents formats like:

- Excel to export grid data
- SBML or XML to export metabolic network
- JSON or HTML link to export visualisation

Take home messages

Take home messages

- Genome-scale metabolic network reconstruction allows to explore metabolism and to map omics data
- Metabolic networks offer a context to interpret omics data
- Graph models is able to infer complex behaviours of metabolic networks alone or in interaction
- MetExplore offers facilities to build, explore, visualise and model the metabolic networks
- MetExplore is part of a wider tool ecosystem

Useful links

- MetExplore website:
<https://metexplore.toulouse.inrae.fr/>
- MetExplore documentation:
<https://metexplore.toulouse.inrae.fr/metexplore-doc/>
- MetExplore tutorial:
<https://metexplore.pages.mia.inra.fr/metexplore-training/>

Thanks to organizers

Thanks to MetExplore team



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IE INRAE



Clément Trainay
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Ludovic Cottret
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CDD IE bioinfo



Jean-Clément Gallardo
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Marion Liotier
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Supplementary data and analysis

PAM50 genes list: signatures for breast cancer subtypes
convert to ensembl with <https://biit.cs.ut.ee/gprofiler/convert>

12 genes mapped in humanGEM

25 reactions on 9 pathways including pyrimidine metabolism -> Thioredoxin and its oxydation

Link between this metabolite and cancer progression and metastasis

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3835076/>

