

VISUALISATION DE RÉSEAUX MÉTABOLIQUES, CONCEPTS ET TECHNIQUES

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French Agronomic and Environment Research Institute (INRAE) Toulouse, FRANCE

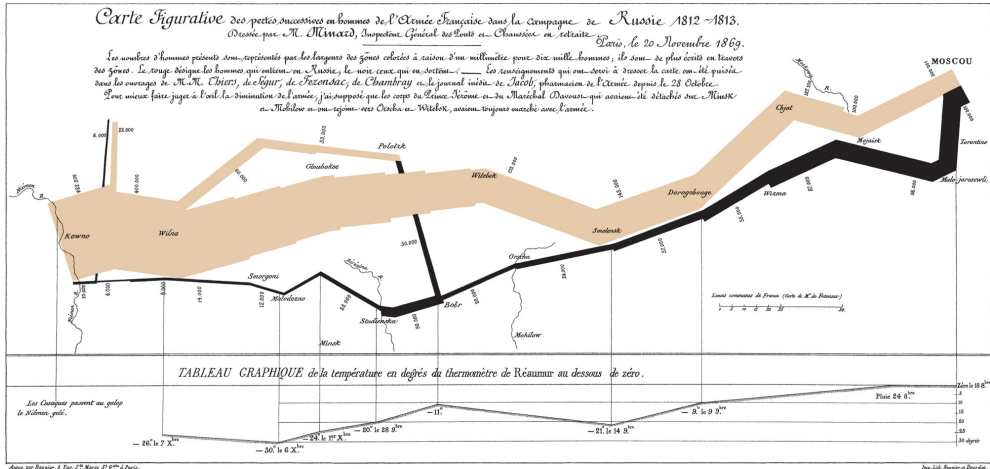
 @MetExplore

 Fabien.Jourdan@inrae.fr

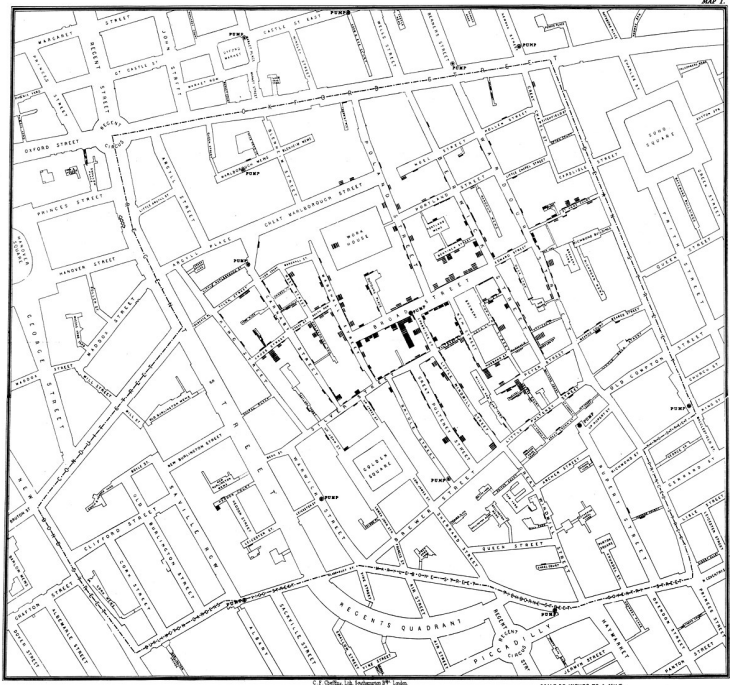


Challenge of data visualisation with no prior knowledge on element localisation

Visualisation



Napoleon russian campaign, 1869 Charles Joseph Minard's representation.

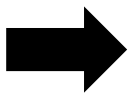


1854 John Snow map during Cholera pandemic in London

Information visualisation

Knowledge

- A-B
- B-C
- C-D
- C-E
-

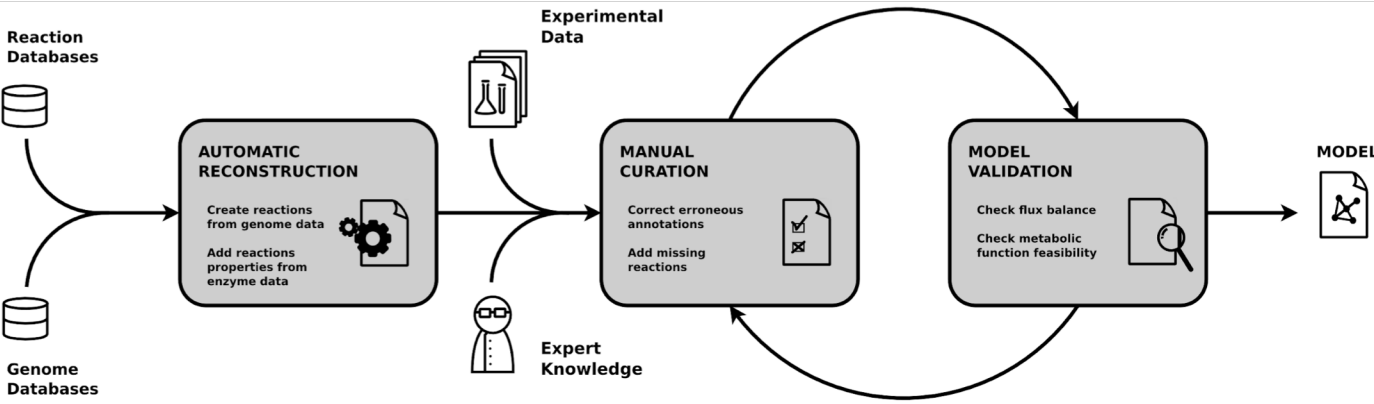


- Which data structure? (**modelling**)
- How to represent the data structure? (**drawing**)
- How to mine representation? (**user interface**)

Apply information visualisation to metabolism

FROM KNOWLEDGE TO GRAPHS

Genome-scale metabolic networks: assembling metabolic information



Reconstruction pipeline

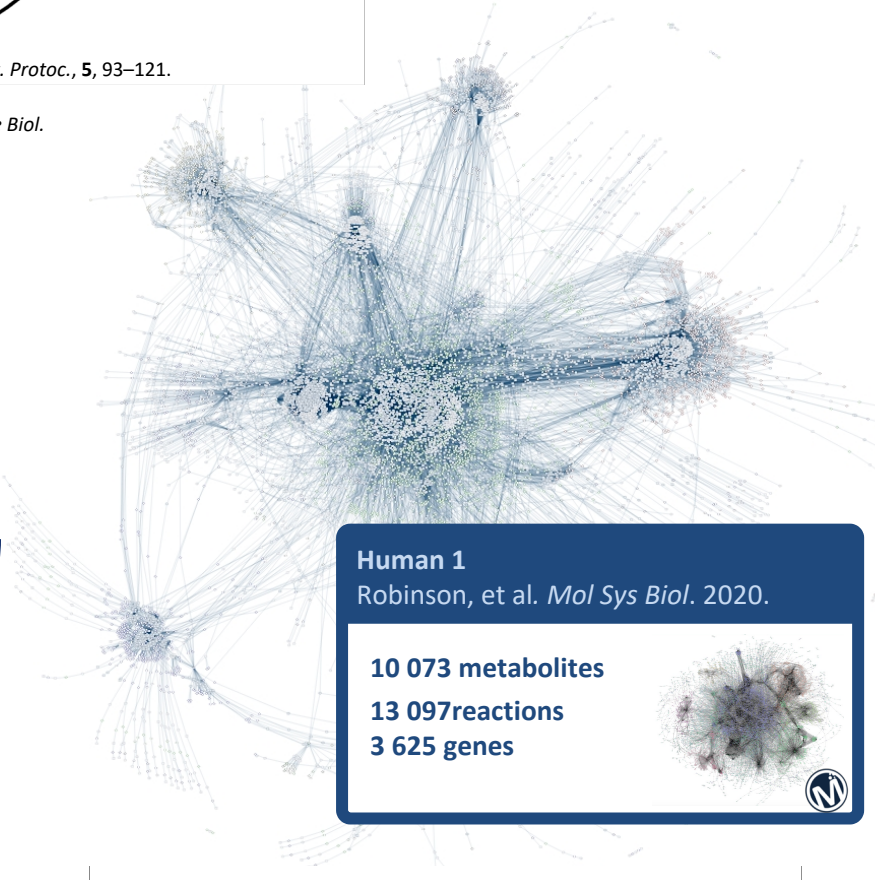
Thiele, I. and Palsson, B.Ø. (2010) A protocol for generating a high-quality genome-scale metabolic reconstruction. *Nat. Protoc.*, 5, 93–121.
 Frainay & Jourdan. *Genome-scale metabolic networks*. (2019). *Metabolomics: Practical Guide to Design and Analysis*.
 Mendoza, S.N. et al. (2019) A systematic assessment of current genome-scale metabolic reconstruction tools. *Genome Biol*.

list of genes

(6524) or (6526)
(3098)
(2821)
(2539)

list of reactions

GLCt4	$Na_e + gluc_e \leftrightarrow Na_c + gluc_c$
HEX1	$gluc_c + ATP_c \rightarrow ADP_c + g6p_c$
PGI	$g6p_c \rightarrow f6p_c$
G6PDH2r	$g6p_c + nadp_c \rightarrow 6pgl_c + nadph_c$
GLCter	$gluc_c \leftrightarrow gluc_r$



Human 1
 Robinson, et al. *Mol Sys Biol*. 2020.

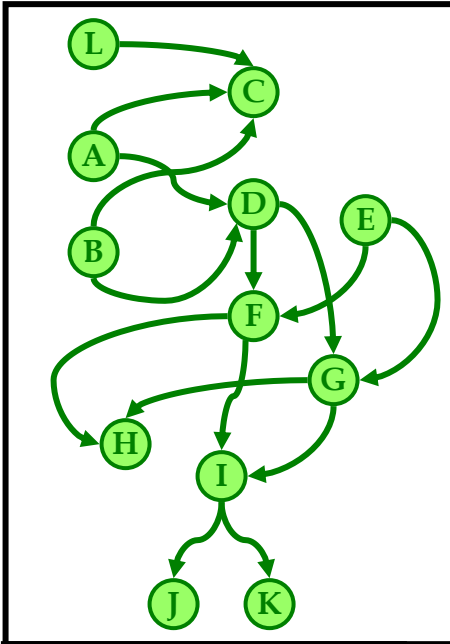
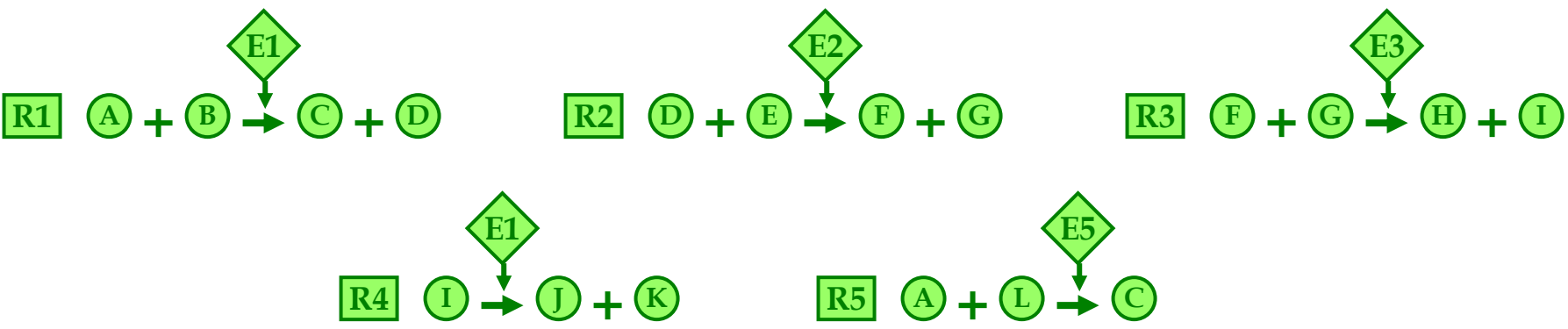
10 073 metabolites
 13 097 reactions
 3 625 genes

DB

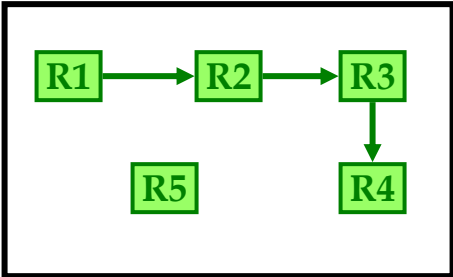
.sbml

Graph modelling(s) of metabolic networks ... a challenge

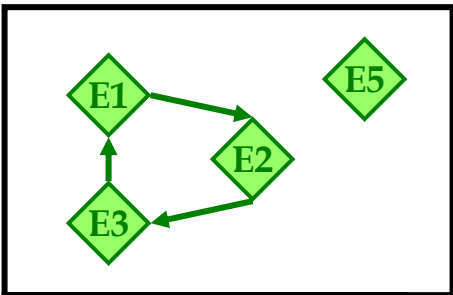
Textual description of the network



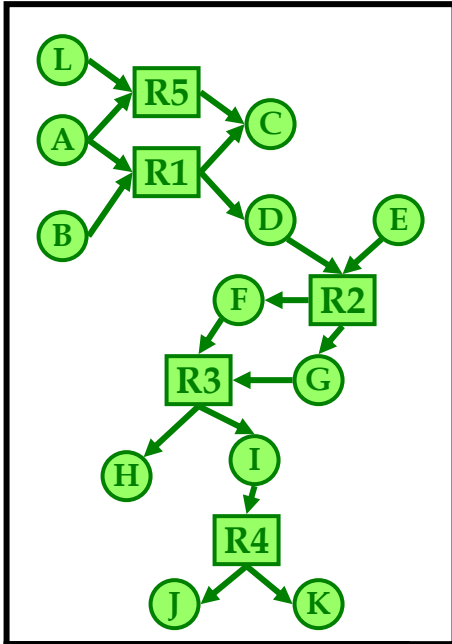
a. Compound graph



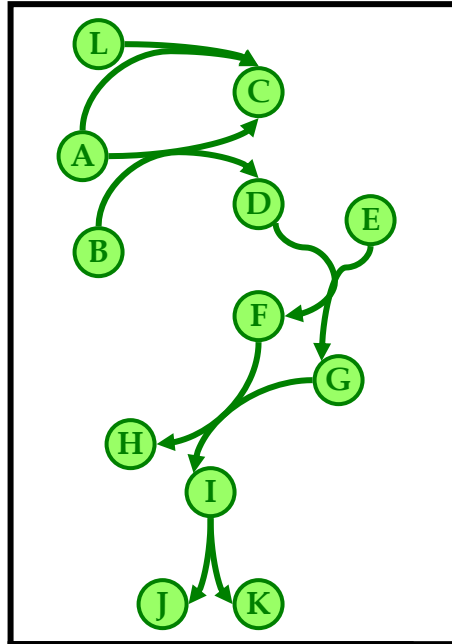
b. Reaction graph



c. Enzyme graph



d. Bipartite graph



e. Hypergraph

METABOLIC GRAPH DRAWING

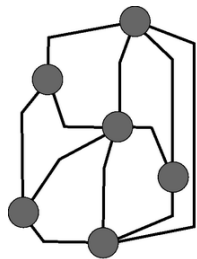
How to draw a metabolic graph?

Graph drawing community

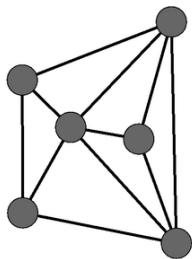
Cognitive Measurements of Graph Aesthetics

Colin Ware, Helen Purchase[#], Linda Colpoys[#] and Matthew McGill[#]

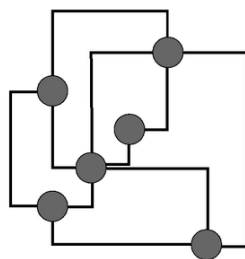
- Continuity (“path bendiness”)(con)
- Number of crossings (cr) and average crossing angles (aca)
- Number of branches (br)
- Shortest path length (spl)
- Total geometric line length (tll)
- Total crossings in the graph (tcr)



A



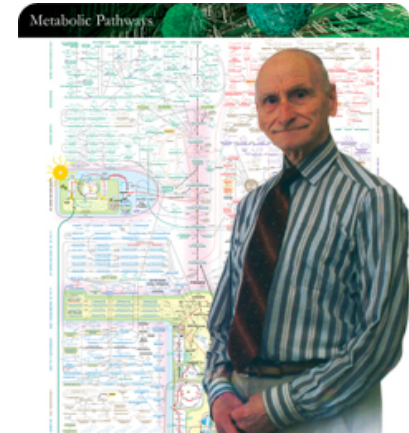
B



C

Biochemists

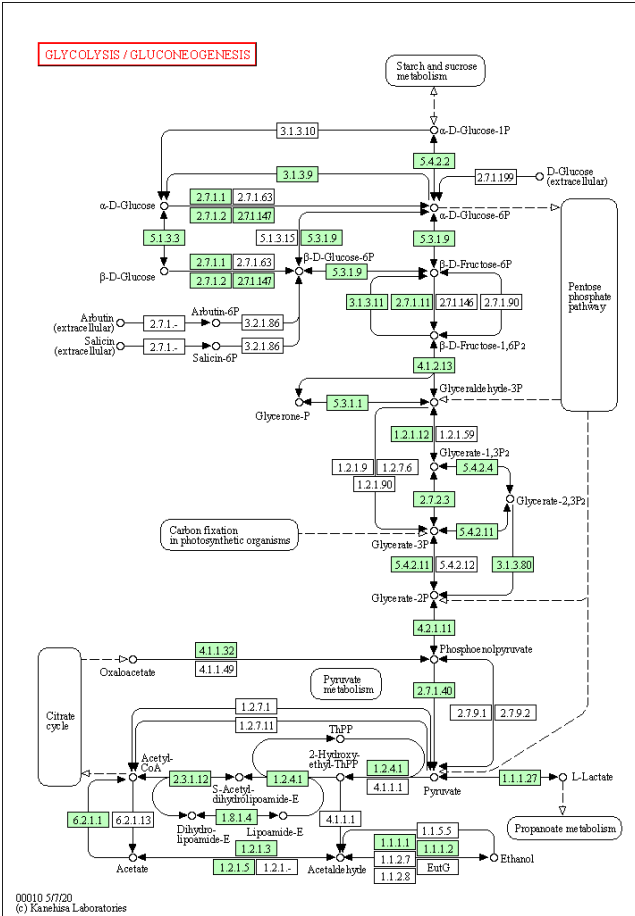
Follow text book conventions!!!



But

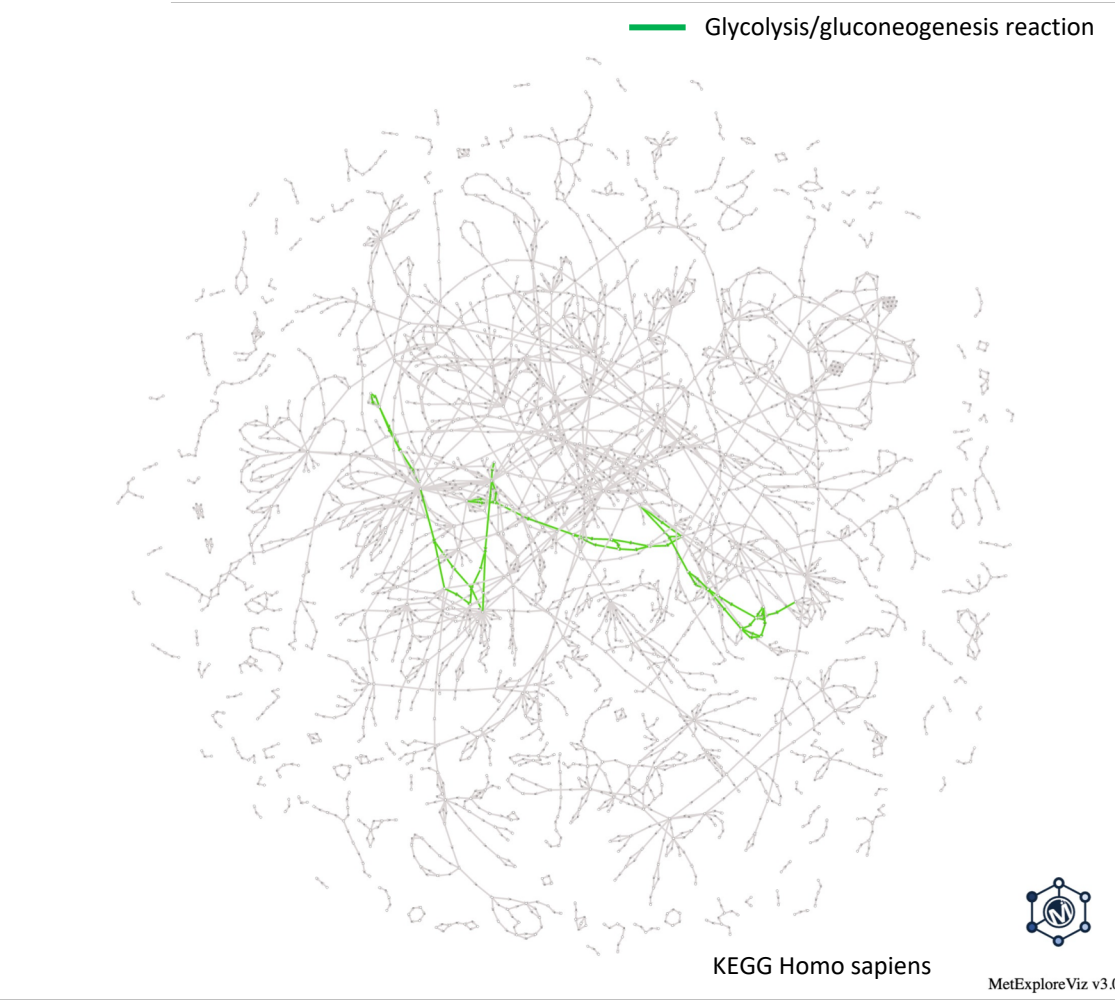
We have to deal with different level of representations: from pathways to network

Pathway: function oriented

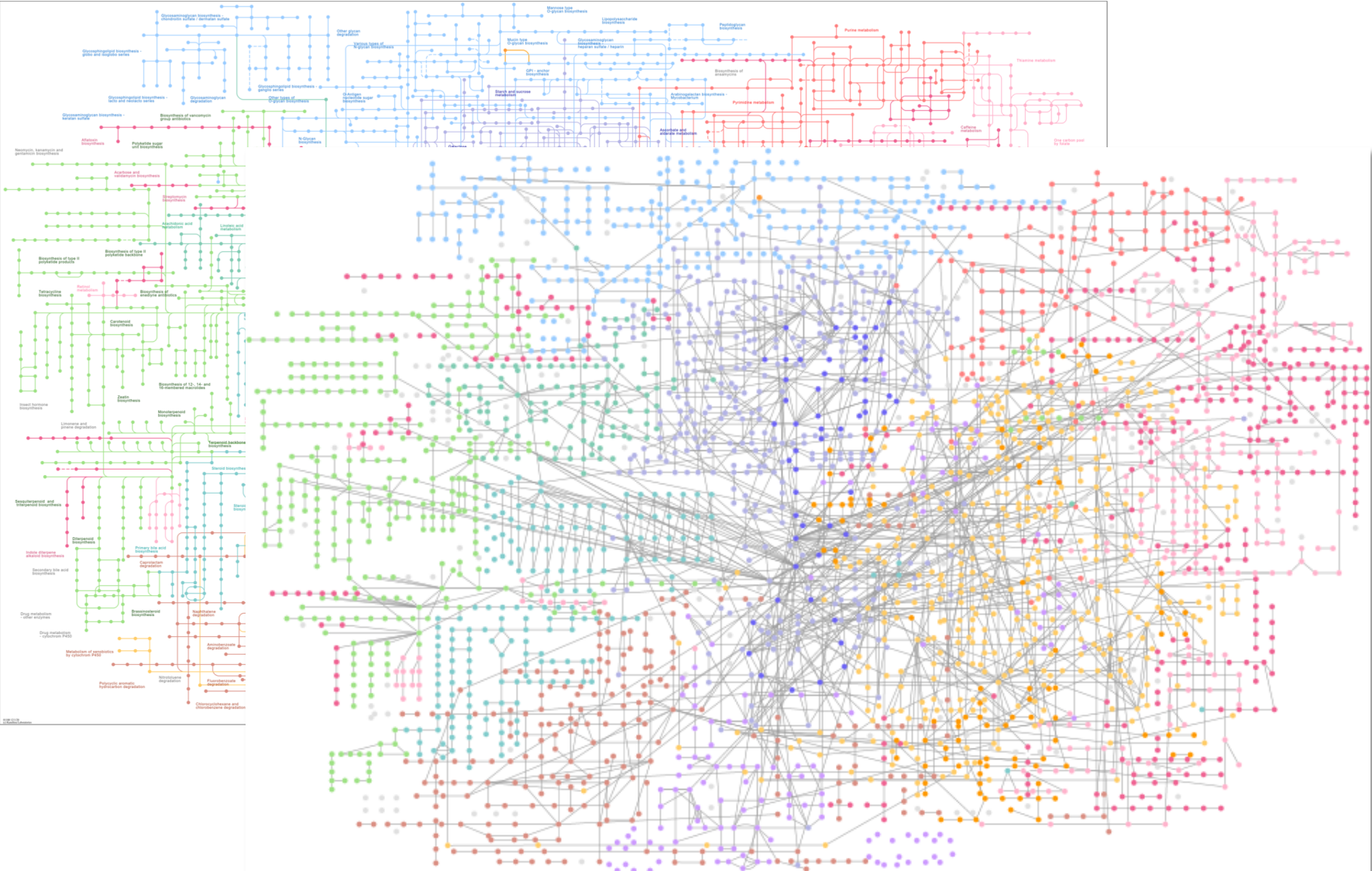


KEGG Homo sapiens

Network: System perspective

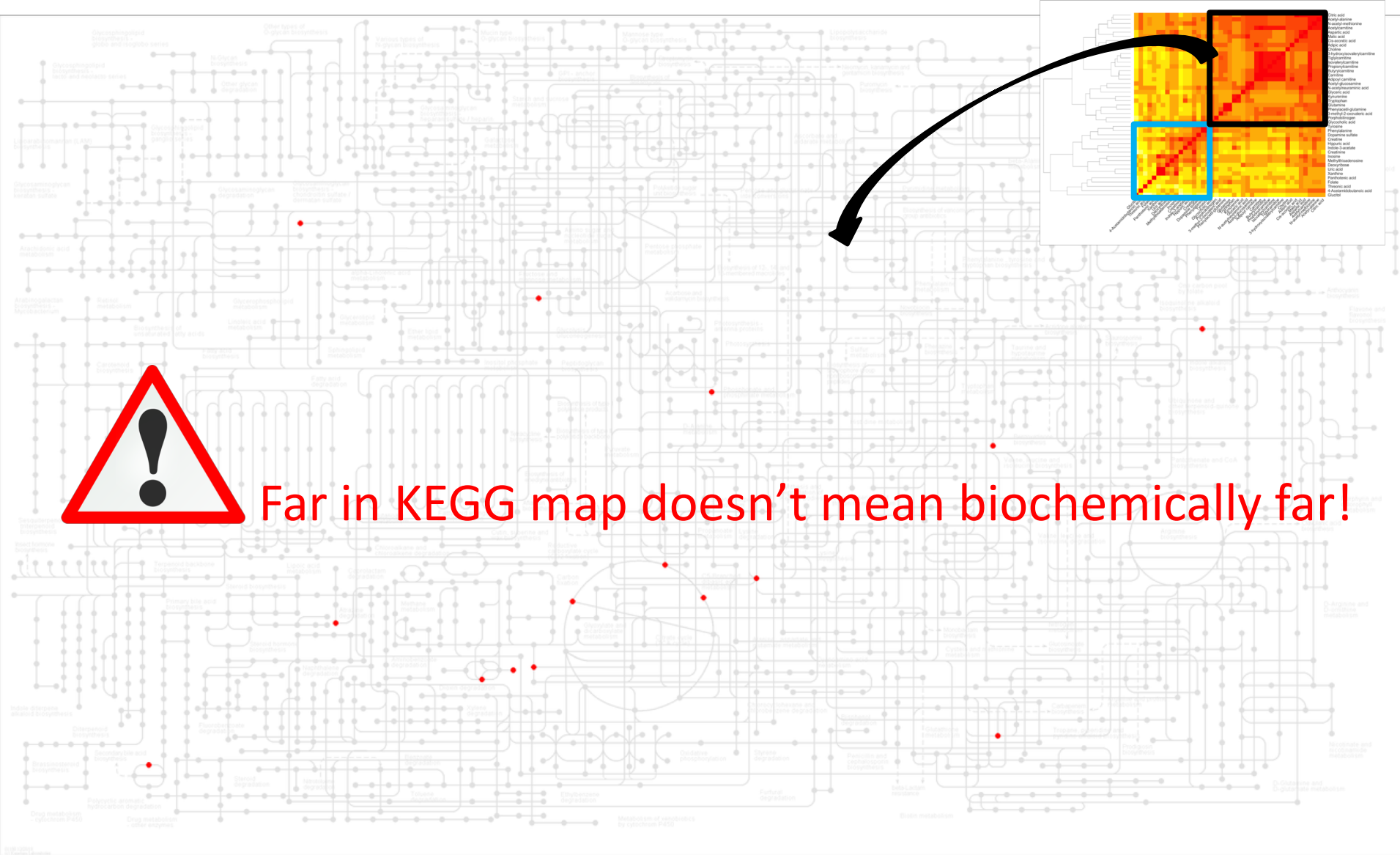


Usually followed option for large scale drawing: remove edges



In reality ...

Representation can be misleading for the interpretation



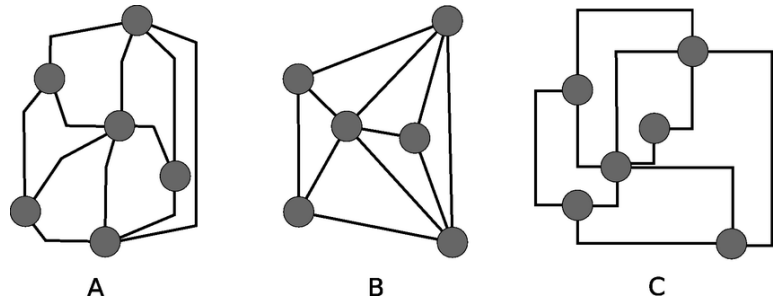
Far in KEGG map doesn't mean biochemically far!

How « good » is a network representation?

Graph drawing community

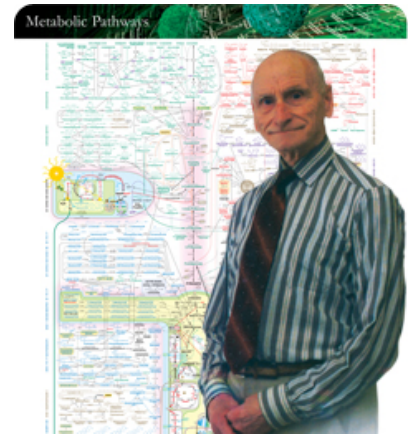
Cognitive Measurements of Graph Aesthetics
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- Continuity (“path bendiness”)(con)
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Biochemists

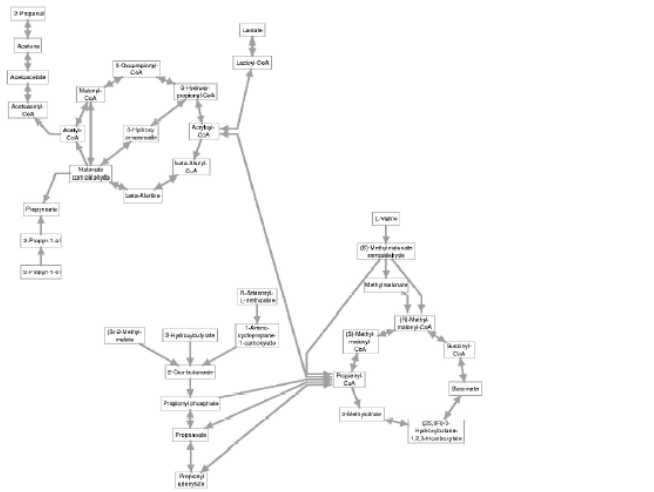
Follow text book conventions!!!



Reality is in between

- Difficult to follow text book conventions at genome scale level (thousands of nodes and edges)
- Nevertheless, we need some visual anchors for metabolism (cycles, paths)
- Take advantage of computational assisted visualisation

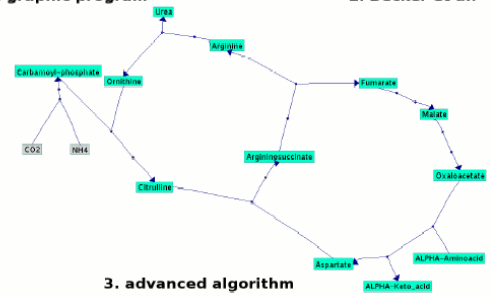
Can we create visualisation following text book conventions and keeping right connectivity?



A Graph Layout Algorithm for Drawing Metabolic Pathways. Moritz Y. Becker and Isabel Rojas. 2001. *Bioinformatics* (17). Pages 461-467



1. graphic program **2. Becker et al.**

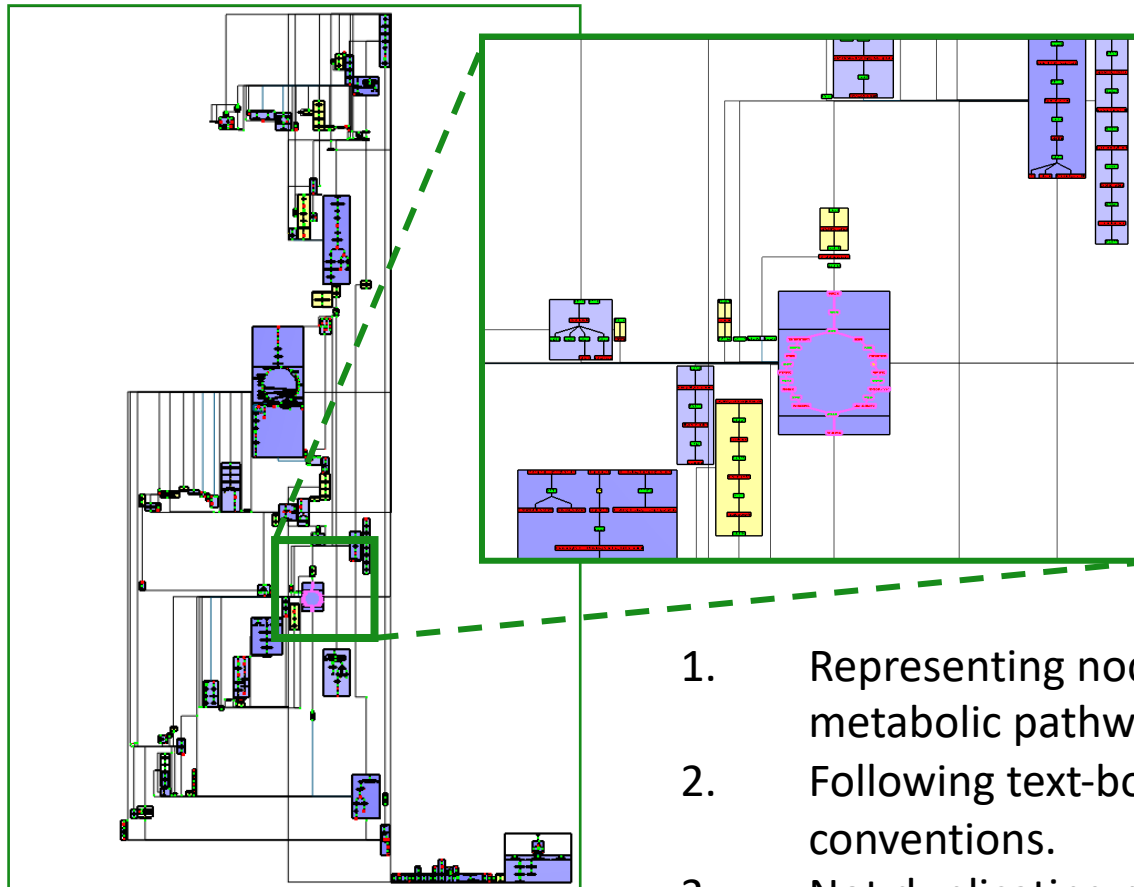


3. advanced algorithm

A new dynamical layout algorithm for complex biochemical reaction networks. Katja Wegner and Ursula Kummer. 2005. *BMC Bioinformatics*.

Doesn't scale

Pathway oriented visualisation without node duplication



1. Representing nodes of the same metabolic pathway close to each other.
2. Following text-book drawing conventions.
3. Not duplicating nodes.

Metabolic network visualization eliminating node redundancy and preserving metabolic pathways

Romain Bourqui, Ludovic Cottret, Vincent Lacroix, David Auber, Patrick Mary, Marie-France Sagot & Fabien Jourdan 

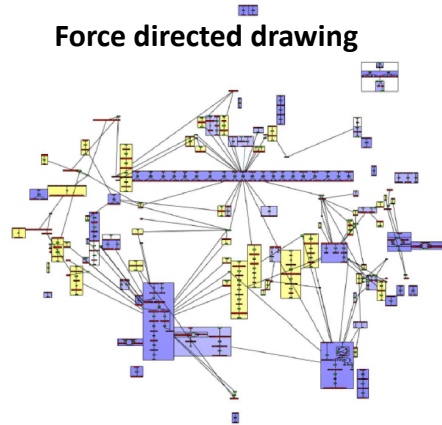
BMC Systems Biology 1, Article number: 29 (2007) | [Cite this article](#)

11k Accesses | 31 Citations | 0 Altmetric | [Metrics](#)

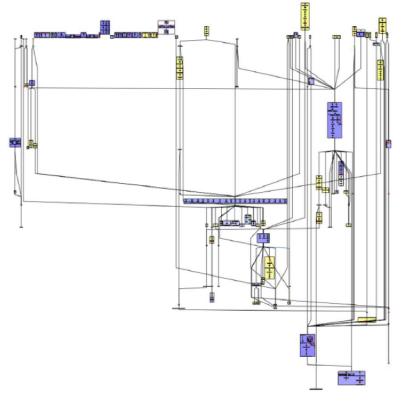
What would be the best option to draw edges between pathways?

Experiments to find the best drawing

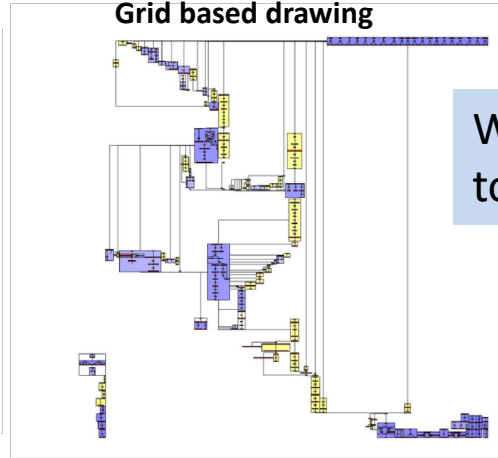
Force directed drawing



Hierarchical drawing



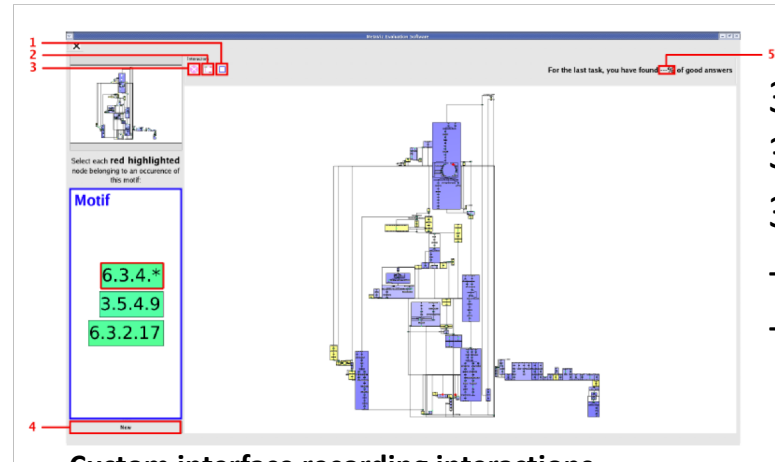
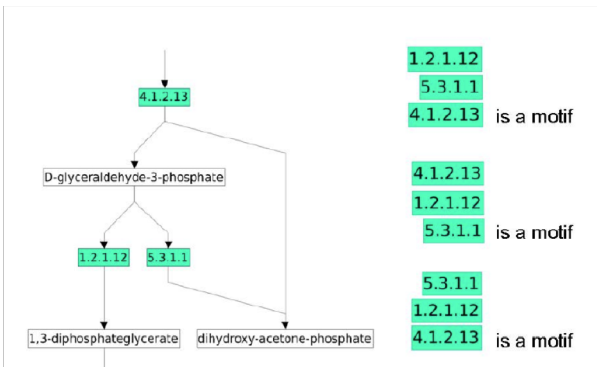
Grid based drawing



Which drawing is the best to achieve a task?

Task: retrieve a motif (group of 3 reactions in the network)

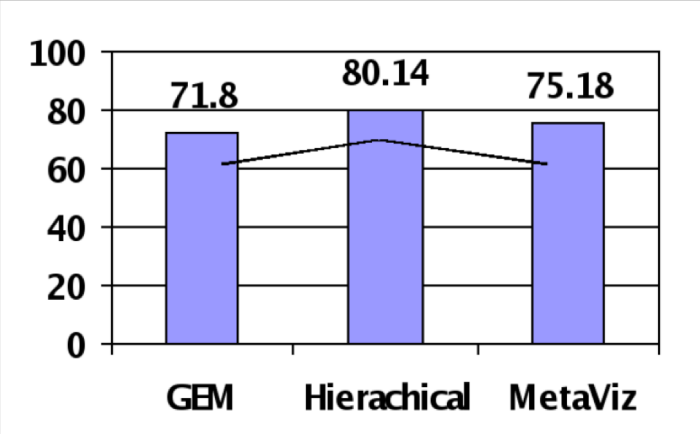
Experimental set-up



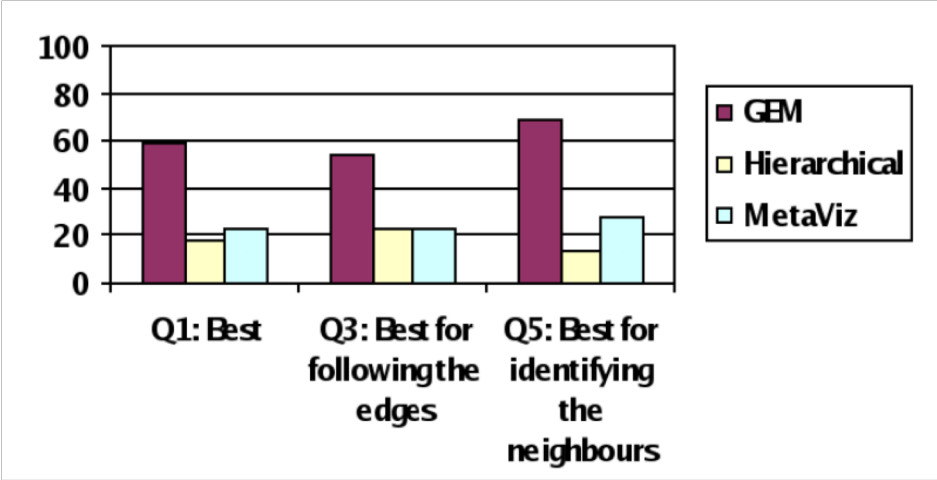
Custom interface recording interactions

3 biological networks
 3 drawings
 3 motifs to search
 -> 27 tasks
 -> 22 participants

Nice is not fully correlated with efficiency



1. The Hierarchical layout produces worst time performance than both the MetaViz and GEM layouts: an average of 80.14s (Hierarchical) versus 71.8s (GEM) and 75.18s (MetaViz).
2. There is no statistical difference in performance between the MetaViz and GEM layouts, despite the average for MetaViz (75.18s) being greater than that of GEM (71.8s).



Results:

- Hierarchical significantly less efficient than the other two
- No significant difference between Force directed and grid based
- Clear preference for force directed

Limits: not performed with biologists (7 bioinformatics, 15 computer science)

Conclusion: visual preference is not necessary correlated with performance!

Next: We need a more flexible strategy including representation manual representation -> MetExploreViz

MetExplore #10YearsChallenge

2009

2019

The image displays two versions of the MetExplore web application. The left window, dated 2009, shows a simple search interface with a sidebar for navigation and a main area for filtering results. The right window, dated 2019, shows a more sophisticated interface with a large, colorful metabolic network diagram and various toolbars for interacting with the data.



Ludovic Cottret



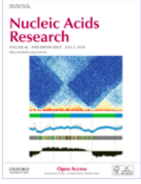
Florence Vinson




Maxime Chazalviel

Nucleic Acids Research

Issues Section browse ▾ Advance articles Submit ▾ Purchase About ▾ All Nucleic Acids Re



MetExplore: collaborative edition and exploration of metabolic networks 

Ludovic Cottret ✉, Clément Frainay, Maxime Chazalviel, Floréal Cabanettes, Yoann Gloaguen, Etienne Camenen, Benjamin Merlet, Stéphanie Heux, Jean-Charles Portais, Nathalie Poupin, Florence Vinson, Fabien Jourdan ✉

Nucleic Acids Research, Volume 46, Issue W1, 2 July 2018, Pages W495–W502,
<https://doi.org/10.1093/nar/gky301>

Published: 30 April 2018 **Article history** ▾



The project

- *Publications* :
 - Cottret et al (2018). *Nucleic Acids Research*
 - Chazalviel et al (2017). *Bioinformatics*
 - Frainay et al (2018). *Bioinformatics*
- *Number of citations*: >120
- *Metrics*:
 - > **840** registered users,
 - > **1500** networks
 - > **700** persons trained
- Involved in several national and EU grants
- 1 industrial partner

Website

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

Functions

- + Collaborative curation of networks
- + omics data mapping
- + Network visualisation
- + graph algorithms
- + Webservices
- + Expertise and user support



<https://forgemia.inra.fr/metexplore/MetExploreViz>

- Dedicated to metabolism visualisation
- Open source
- Javascript library
- Web-component like

Include the library

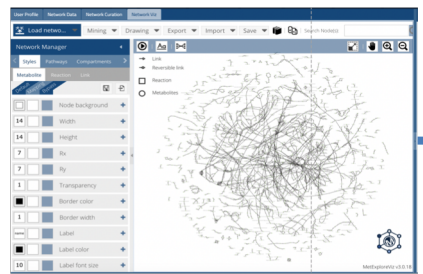
Include the release in your website:

```
<script type="text/javascript" src="YOUR-FOLDER/metExploreViz/metexploreviz.js" charset="utf-8">
</script>
```

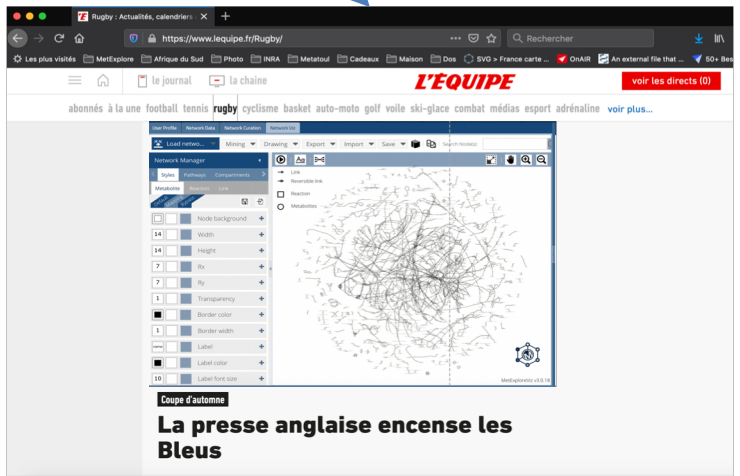
Launch the window

Include the release in your website:

```
<script type="text/javascript">
  MetExploreViz.initFrame("YOUR-DIV-ID");
</script>
```



Component like: embed in your own website



Bioinformatics, 34(2), 2018, 312–313
 doi: 10.1093/bioinformatics/btx588
 Advance Access Publication Date: 15 September 2017
 Applications Note



Systems biology

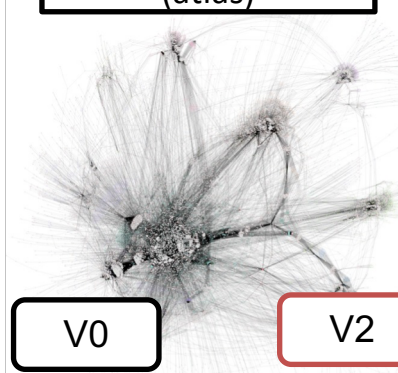
MetExploreViz: web component for interactive metabolic network visualization

Maxime Chazalviel^{1,2}, Clément Frainay¹, Nathalie Poupin¹,
 Florence Vinson¹, Benjamin Merlet¹, Yoann Gloaguen³, Ludovic Cottret⁴
 and Fabien Jourdan^{1,*}

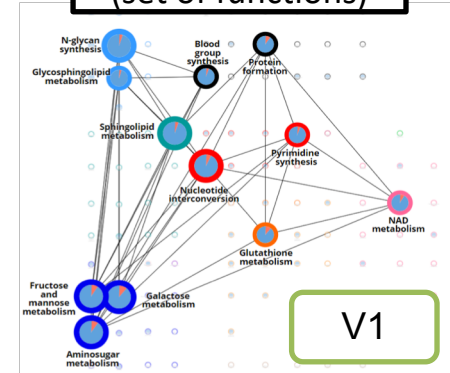


Overview

Network oriented (atlas)



Pathway oriented (set of functions)



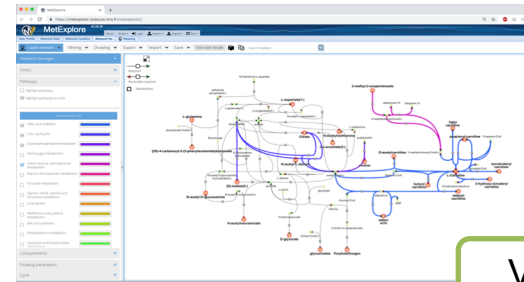
Filter

Sub-network extraction

V1

Pathway selection

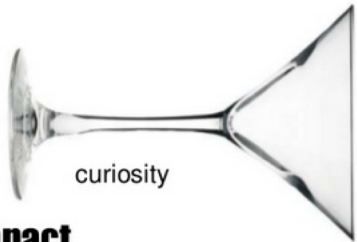
V0



Details on demand

V2: AI driven exploration

Overview first, Zoom and Filter, Details-on-demand



exploration personalisation

Ben Schneiderman

MetExploreViz, overview first

Export: json, gml, svg...

The screenshot shows the MetExplore v2.27.5 interface. At the top, there is a navigation bar with 'About', 'Omics', 'Toolbox', 'Import', 'Export', and 'Login'. Below this is a 'Network Manager' section with tabs for 'Styles', 'Pathways', and 'Compartments'. The 'Styles' tab is active, showing a list of customizable properties for nodes and links, such as 'Node background', 'Width', 'Height', 'Rx', 'Ry', 'Transparency', 'Border color', 'Border width', 'Label', 'Label color', and 'Label font size'. The central area displays a complex network graph with nodes and edges. To the right, there is a 'Selected BioSource' panel with a table of metabolites and their identifiers.

name	dbIdentifier
(1R)-hydroxy-[2R]-glutathionyl-1,2-dihydronaphthalene glutathione-l...	R07002
(2-naphthyl)methanol:NAD+ oxidoreductase	R06927
(24R,25R)-3alpha,7alpha,12alpha,24-tetrahydroxy-5beta-cholestano...	R04813
(24S)-cholest-5-ene-3beta,7alpha,24-triol:NAD+ 3-oxidoreductase	R08721
(25S)-3alpha,7alpha-dihydroxy-5beta-cholestanoyl-CoA:acceptor 24,...	R08740
(25S)-3alpha,7alpha,12alpha-trihydroxy-5beta-cholestan-26-oyl-Co...	R08735
(2E,6E)-farnesyl-diphosphate:isopentenyl-diphosphate cistransferase...	R05556
(2E,6E)-farnesyl-diphosphate:isopentenyl-diphosphate farnesyltranst...	R09249
(2R)-3-sulfolactate:NAD+ oxidoreductase	R07136
(2S,3S)-3-Hydroxy-2-methylbutanoyl-CoA hydro-lyase	R04204
(2S,3S)-3-Hydroxy-2-methylbutanoyl-CoA:NAD+ oxidoreductase	R04203
(2S)-ethylmalonyl-CoA epimerase	R09979
(3R)-3-Hydroxybutanoyl-[acyl-carrier protein]:NADP+ oxidoreductase	R04533
(3R)-3-Hydroxybutanoyl-[acyl-carrier-protein] hydro-lyase	R04537
(3R)-3-Hydroxybutanoyl-[acyl-carrier-protein] hydro-lyase	R04954
(3R)-3-Hydroxybutanoyl-[acyl-carrier-protein] hydro-lyase	R04965
(3R)-3-Hydroxybutanoyl-[acyl-carrier-protein] hydro-lyase	R04428
(3R)-3-Hydroxybutanoyl-[acyl-carrier-protein] hydro-lyase	R04535
(3R)-3-Hydroxydecanoyl-[acyl-carrier-protein]:NADP+ oxidoreductase	R04534
(3R)-3-Hydroxydodecanoyl-[acyl-carrier-protein]:NADP+ oxidoreducta...	R04964

Fully customizable view (cytoscape like)

D3Js, force based alorighm

Create your own network by reaction selection

Subnetwork extraction

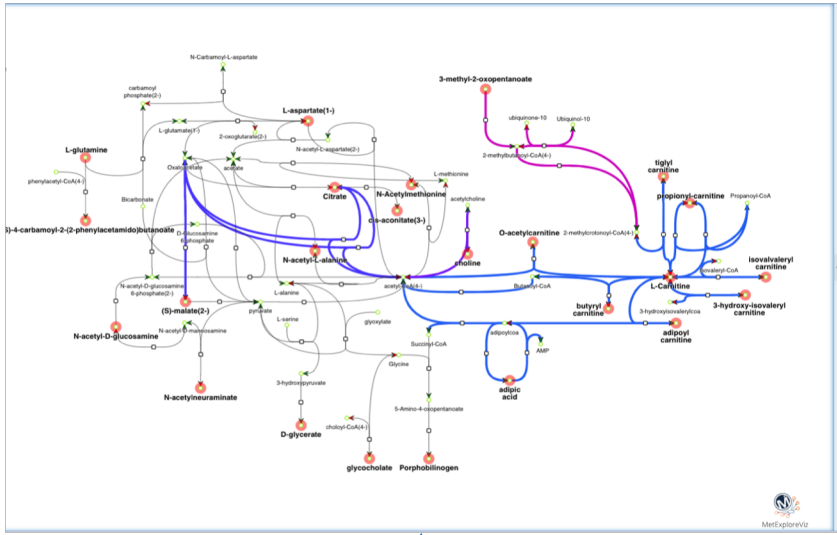
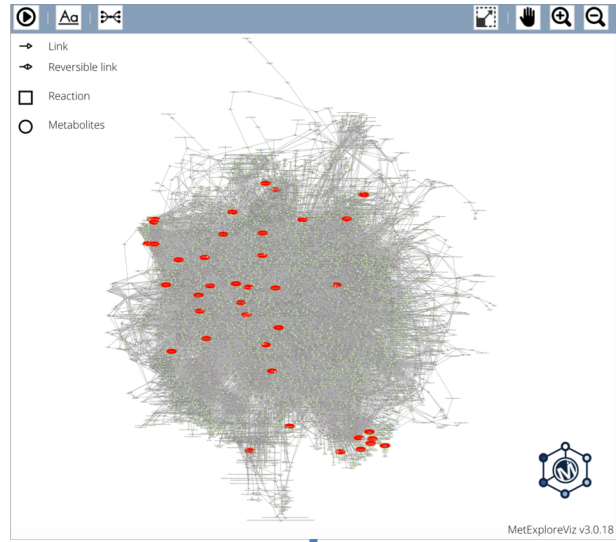
Journal of Inherited Metabolic Disease
<https://doi.org/10.1007/s10545-017-0134-3>

METABOLOMICS



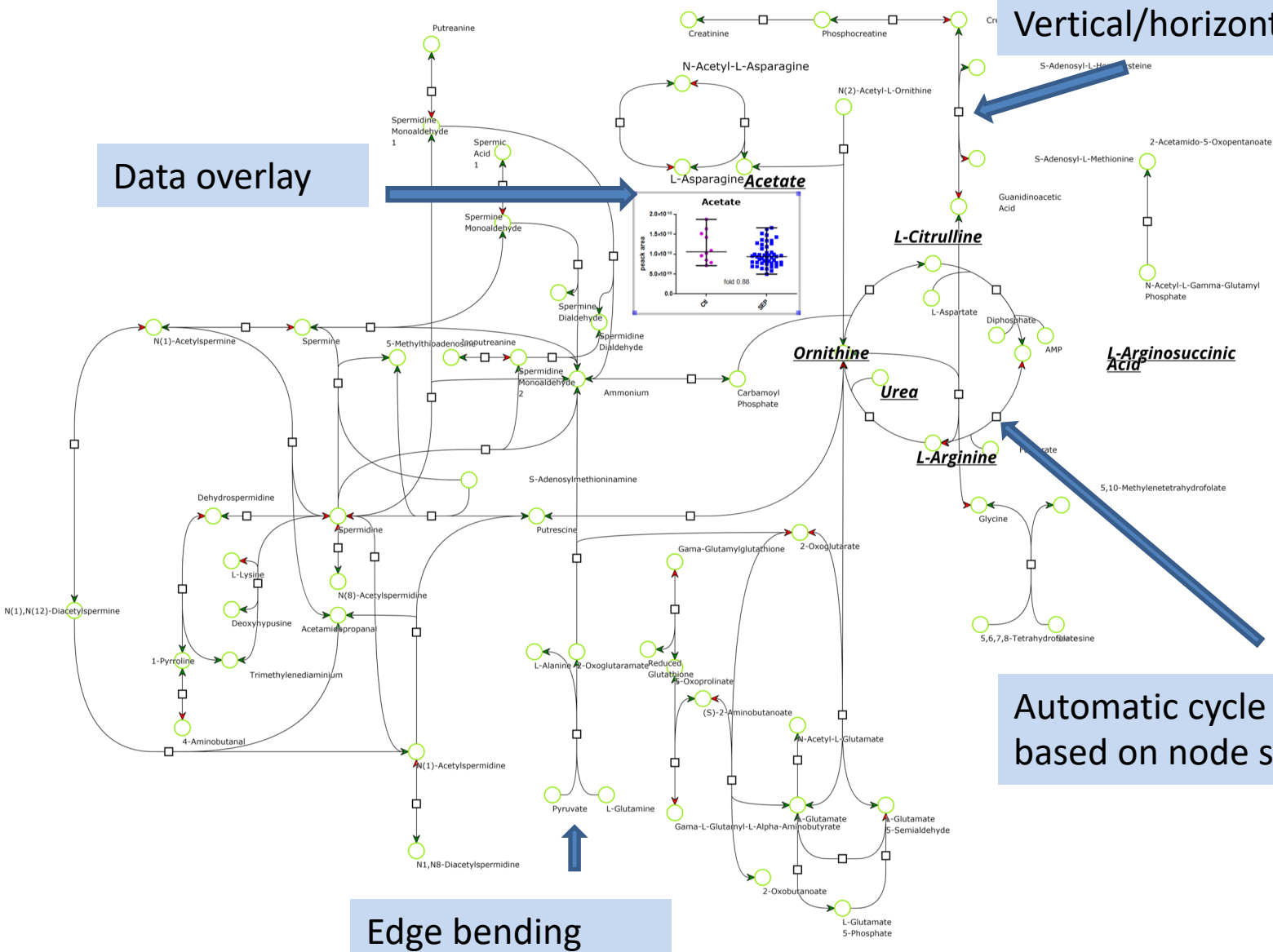
Targeted versus untargeted omics — the CAFSA story

Maria del Mar Amador¹ • Benoit Colsch² • Foudil Lamari^{3,4} • Claude Jardel^{3,4} • Farid Ichou⁵ • Agnès Rastetter⁶ • Frédéric Sedel⁷ • Fabien Jourdan⁸ • Clément Frainay⁸ • Ronald A. Wevers⁹ • Emmanuel Roze^{1,4,6} • Christel Depienne¹⁰ • Christophe Junot² • Fanny Mochel^{4,6,11,12}



Subnetwork extraction based on shortest path search in carbon transfer graph

Cycle detection and representation



Data overlay

Vertical/horizontal layout

Automatic cycle detection based on node selections

Edge bending

Work done by Adrien Rohan

Fabien JOURDAN © 2020





Dr. Nathalie Poupin
INRAE researcher

Journal of proteome research

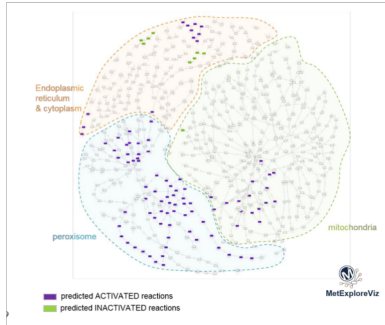
Subscriber access provided by INRA Institut National de la Recherche Agronomique

Article

A large-scale modelling approach reveals functional metabolic shifts during hepatic differentiation

Nathalie Poupin, Anne Corlu, Nicolas J. Cabaton, Hélène Dubois-Pot-Schneider, Cécile Canlet, Elodie Person, Sandrine Bruel, Clément Frainay, Florence Vinson, Florence Maurier, Fabrice Morel, Marie-Anne Robin, Bernard Fromenty, Daniel Zaiko, and Fabien Jourdan

J. Proteome Res., Just Accepted Manuscript • DOI: 10.1021/acs.jproteome.8b00524 • Publication Date (Web): 05 Nov 2018



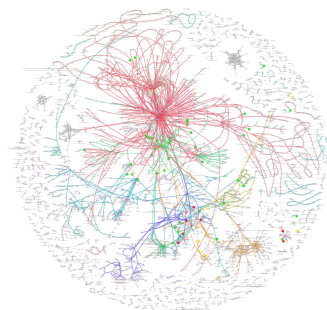
Reaction data mapping

Metabolomics (2020) 16:44
https://doi.org/10.1007/s11306-020-01663-5

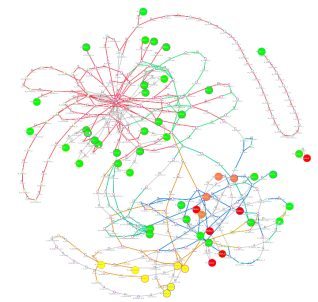
ORIGINAL ARTICLE

Improving lipid mapping in Genome Scale Metabolic Networks using ontologies

Nathalie Poupin¹ · Florence Vinson¹ · Arthur Moreau¹ · Aurélie Batut² · Maxime Chazalviel³ · Benoit Colsch⁴ · Laetitia Fouillen⁵ · Sarah Guez² · Spiro Khoury⁶ · Jessica Dalloux-Chioccioli² · Anthony Tournadre² · Pauline Le Faouder² · Corinne Pouyet⁶ · Pierre Van Delft⁵ · Fanny Viars² · Justine Bertrand-Michel² · Fabien Jourdan¹



Sub-network extraction using "lightest-path" algorithm



18 metabolic pathways including at least 1 mapped metabolites → 2345 reactions

→ 231 reactions

Lipid/metabolite mapping

www.nature.com/scientificreports

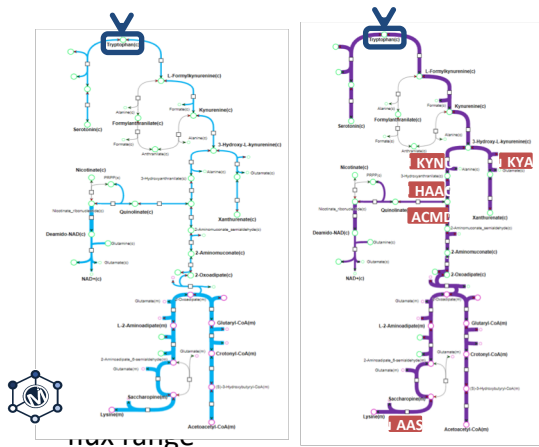
SCIENTIFIC REPORTS

nature research

OPEN

Arterio-venous metabolomics exploration reveals major changes across liver and intestine in the obese Yucatan minipig

Nathalie Poupin¹, Marie Tremblay-Franco¹, Aurélien Amiel^{1,4}, Cécile Canlet^{1,4}, Didier Rémond⁵, Laurent Debrauwer⁵, Dominique Dardevet⁵, Ines Thiele^{1,4,5}, Malika K. Aurich³, Fabien Jourdan¹, Isabelle Savary-Auzeloux⁶ & Sergio Polakof¹



Flux mapping

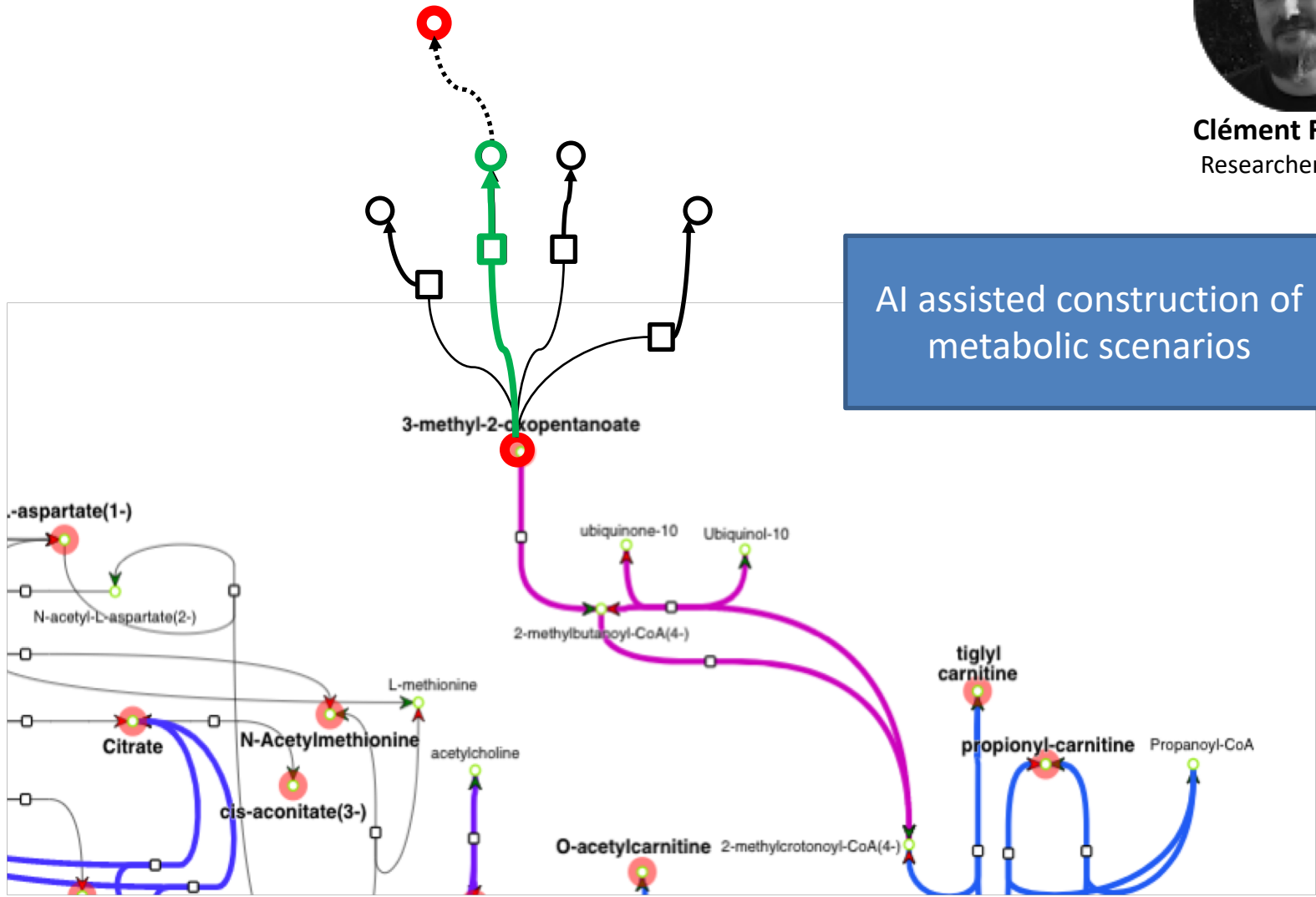


Degree Of Interest : AI (Augmented Intelligence)



Clément Frainay
Researcher INRAE

AI assisted construction of metabolic scenarios



- Don't mix « nice » and « efficient »
- Think about task first
- Include the navigation (UI and computatoin) in the visualisation design
- Challenges:
 - Interop. (identifiers)
 - Interop. (network viz files)
 - Challenge: combine hand drawn visualisation at a larger scale
 - Integrate regulation networks
- Online solutions sounds promising, web component to allow flexibility (MetaboHub objective)
- Plenty of visualisation techniques to combine with network visualisation
- MetExploreViz, open to contributions!



Le beau c'est relatif ...



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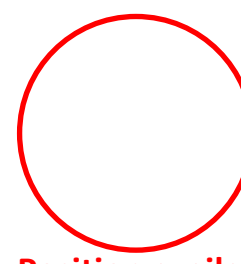
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Position available:
Software dev.: InfoViz



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