How visualization of flux modes helps to generate biochemical hypotheses

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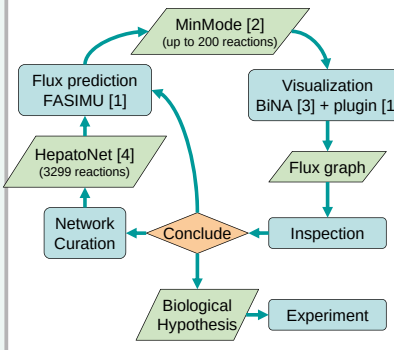
Summary:

The cellular metabolism is traditionally displayed as a number of metabolic pathways. However, proteomics or transcriptomics data show patterns of expressed enzymes that often do not follow conventional pathways. But a clear graphical representation of large scale networks (>1000 reactions) as a whole is an almost infeasible and eventually not necessary task. Meanwhile, flux distributions for specific metabolic objectives predicted by FBA, e.g. MinModes, with a more reasonable size (<200 reactions) are a valuable alternative to tackle and comprehend network utilization.

The visualization tool **BiNA** combined with FBA software developed by the authors is ideally suited to automatically visualize such minimal flux modes: BiNA provides state-of-the-art automatic graph-layout algorithms for comprehensive, interactive network visualization. Flux rates, concentration values or expression data can be represented e.g. by arrow-thickness and colors. Cellular compartmentalization is reflected by network topology or by color.

Here, we present a **work flow**: from the prediction of flux distributions to a testable hypothesis on a previously unknown interaction pattern of enzymes using automatic layout, manual refinement and manual inspection. This hypothesis can be refined by repeating the process with additional constraints. We show how the purposive selection of visual elements increases the lucidity of the graphical representation in a current research example of the human hepatocyte.



What a visualization software should provide:

- autolayout for reasonable startup graph
- greyout/hide reactions with zero flux rate
- zapping through precomputed flux modes
- represent cofactors as aliases
- walk along connected metabolites or reactions
- functional and physical subnetwork separation
- change representation by zooming
- support of a scripting language / user defined functions
- user-friendly and powerful (layout) editing functions
- map flux rate to arrow color or thickness
- map expression levels on reaction boxes
- annotation of nodes (context menus, weblinks)
- customization of graphical node attributes
- customization of mapping attributes

Intake of glucose instead of fat.
Modification of systems boundary!

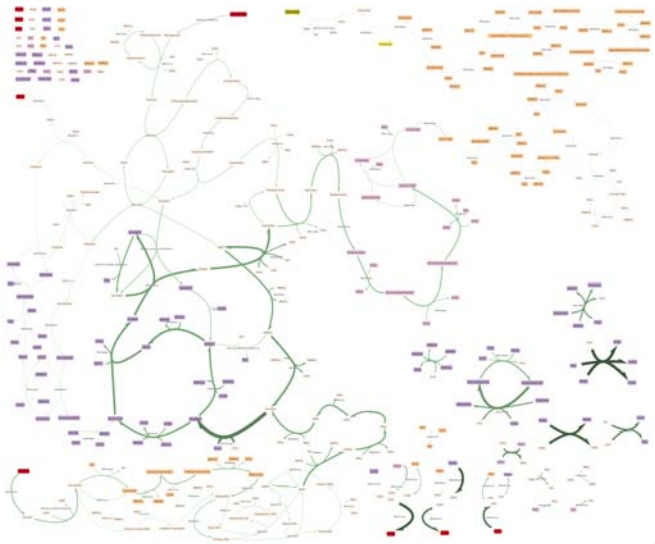
Flux map of the MinMode producing bile cholesterol from minimal exchange set

Cholesterol should not travel through lysosome.
Further network curation!

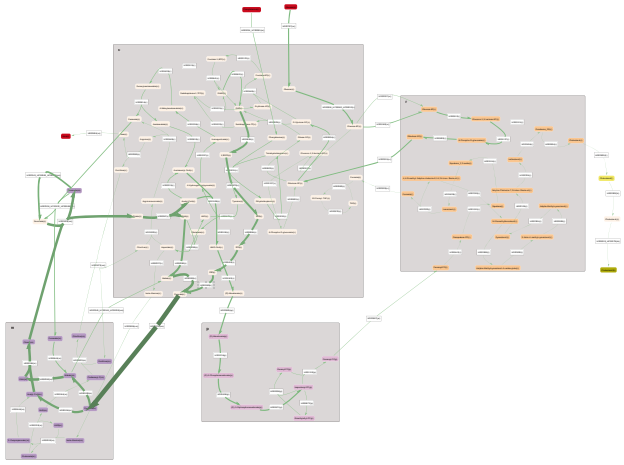
Pentose phosphate pathway has not sufficient capacity.
Modify computational script!

Amino-acid degradation to urea.
Testable hypothesis!

Fluxmap with explicit cofactors



Fluxmap with separated compartments



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References:

1. Hoppe et al. (2010). FASIMU: flexible software for flux-balance computation series in large metabolic networks. Submitted.
2. Hoffmann et. al (2006). Composition of Metabolic Flux Distributions by Functionally Interpretable Minimal Flux Modes (MinModes). Genome Informatics, 17(1), 195-207.
3. Küntzer et al. (2006). BN++ - a biological information system. J Integr Bioinformatics, 3(2), 34.
4. Gille, Bölling, Hoppe et al. (2010), A stoichiometric model of the human hepatocyte. In revision.