Developing a physiological map as a framework to study chemical-induced liver steatosis

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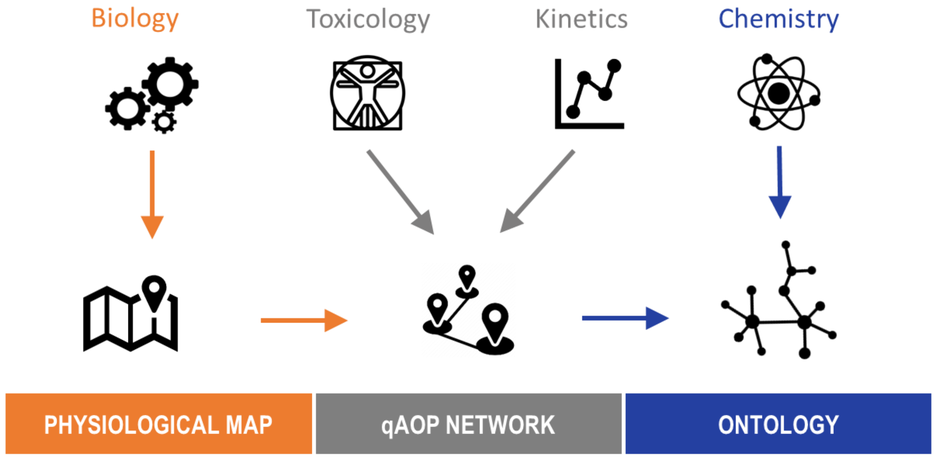
Introduction

Physiological Maps (PMs) are conceptual constructs that integrate knowledge as mechanistic representations of biological processes [1]. PMs can be used qualitatively and quantitatively as a mechanistic background in Adverse Outcome Pathways (AOP) creation and refinement, supporting model rationale, and to develop computational models serving different purposes.

We developed a liver lipid metabolism PM to serve as a framework to improve a steatosis AOP network and build an **ontology** [1] for the study of chemical-induced steatosis.

Roadmap for Toxicological Ontologies establishment:



Methods

We adapted the workflow from the Disease Maps project [2] to construct our PMs.

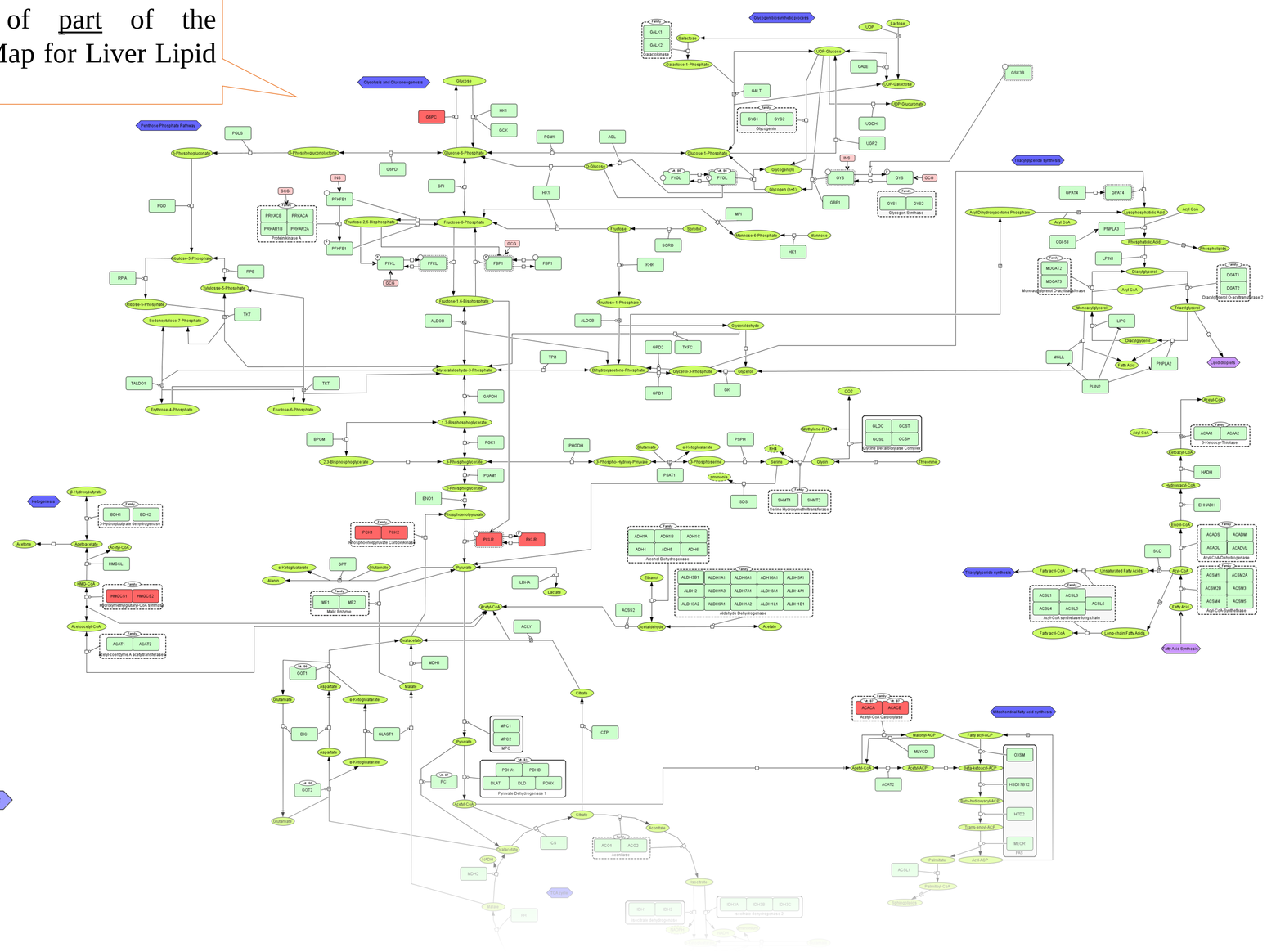
- First, relevant physiological literature was curated with the help of domain experts.
- Next, we listed the fundamental mechanisms to be mapped and screened online databases (e.g. Wikipathways, Reactome, KEGG) for previously described pathways.
- Finally, we integrated pathways and data from the literature using the CellDesigner software, exported as SBML (Systems Biology Markup Language) and displayed them using the MINERVA platform [3].

Results

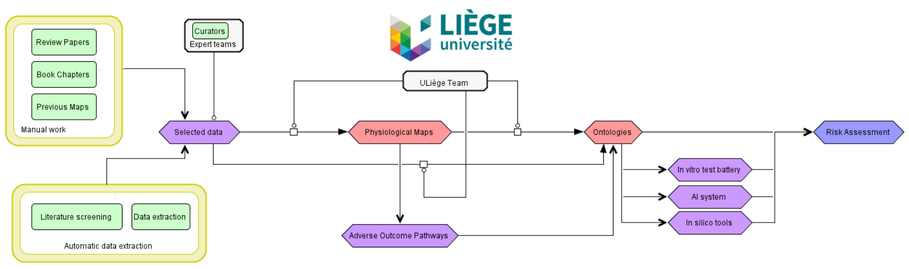
- Expert-curated;
- Human physiology-oriented network;
- Qualitative and Quantitative layers;
- Covers the current steatosis AOP;
- Continuously updated.
- Key mechanisms described:

1. fatty acids uptake,
2. fatty acids synthesis,
3. triacylglycerol synthesis,
4. cholesterol synthesis, and
5. glycolysis (as input);
6. mitochondrial beta-oxidation,
7. peroxisomal beta-oxidation,
8. microsomal omega-oxidation,
9. ketogenesis, and
10. very-low-density lipoproteins (VLDL) secretion (as output);
11. hormones and transcriptional factors (as regulators).

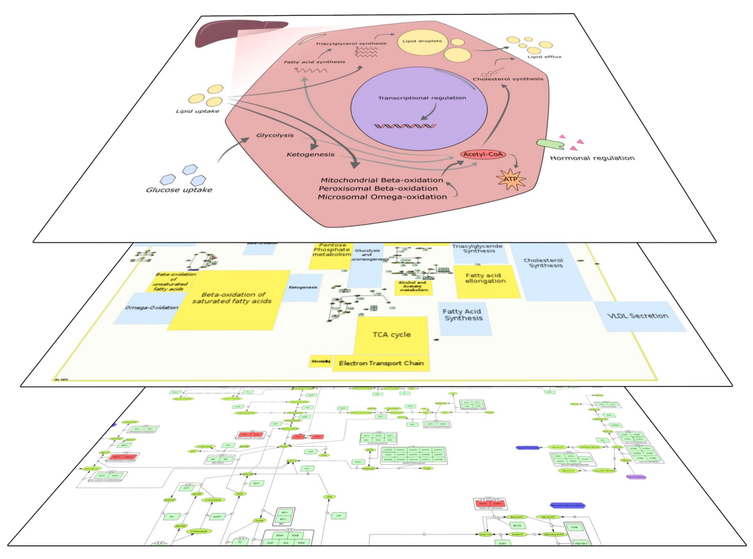
An example of part of the Physiological Map for Liver Lipid Metabolism.



A summary of ONTOX workflow focusing on the ULiège tasks.



Future steps



Graphical concept of the ONTOX liver ontology

PMs are cornerstones to create **ontologies**, integrating different layers of pathological, toxicological, and chemical information, and quantitative kinetic data.

They will contribute to:

(1) better understand organ- and disease-specific pathways in response to chemicals;
(2) visualize omics datasets;
(3) develop quantitative methods for disease modelling and for predicting toxicity;
(4) set up an *in vitro* & *in silico* test battery to detect a specific type of toxicity;
(5) develop new **animal-free approaches** for **next generation risk assessment**.

These tools will be continuously updated, resulting from expert curation and revision in an open community effort.

References

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