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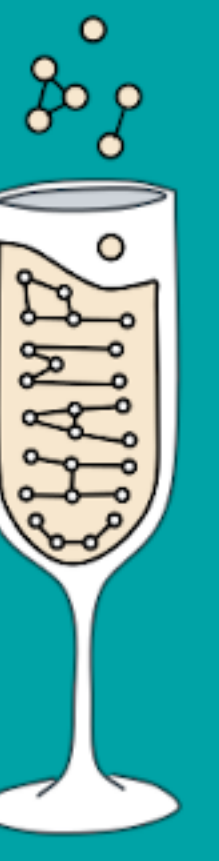
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# The CHaMP web-app: an interactive tool to infer biotransformation pathways from your MS peaks



Marine Valleix<sup>1,2</sup>, Clément Frainay<sup>1</sup>\*, Elodie Person<sup>1</sup>, Jean-François Martin<sup>2</sup>, Laurent Debrauwer<sup>2</sup>, Daniel Zalko<sup>1</sup>, Fabien Jourdan<sup>1</sup> and Sylvie Chevolleau<sup>2</sup>

CONTEXT



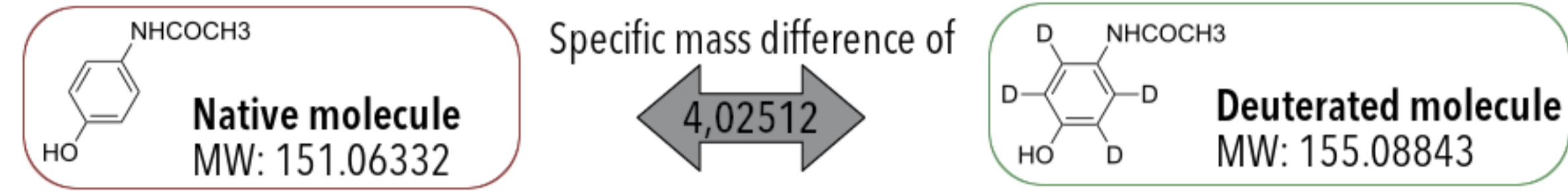
The fate of exogenous compounds within an organism has numerous applications of high societal impact.

High resolution mass spectrometry is a powerful technique to detect biotransformation products. Nevertheless, it generates a large amount of data which must be confronted with a large set of possible transformations to elucidate the involved pathways.

We propose CHaMP, an open source interactive tool to facilitate this tedious yet crucial process.

DATASET CREATION

An equimolar mix of both native and isotope labelled molecules



A metabolically competent system\*

Rat male S9 subcellular fractions n=3 (contains both microsomal and cytosolic enzymes)

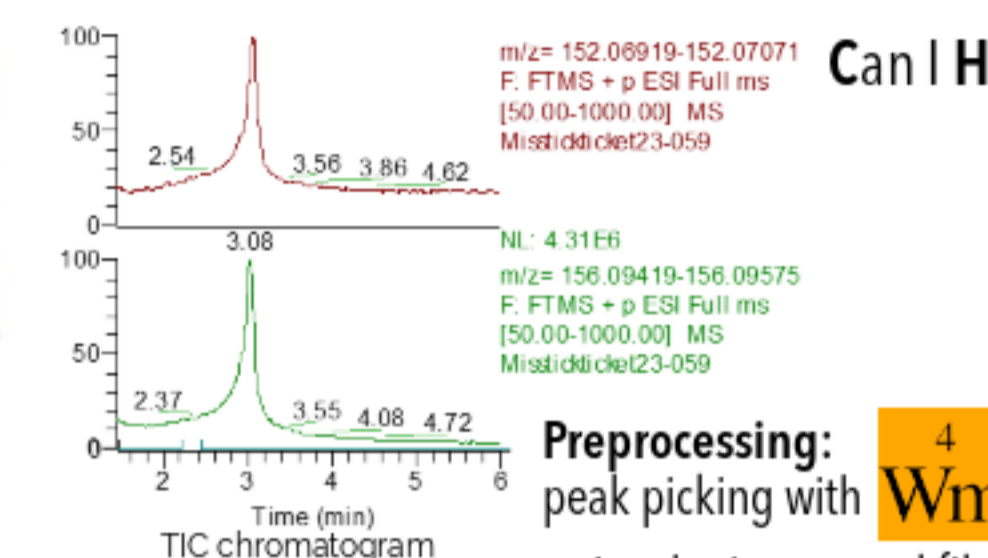
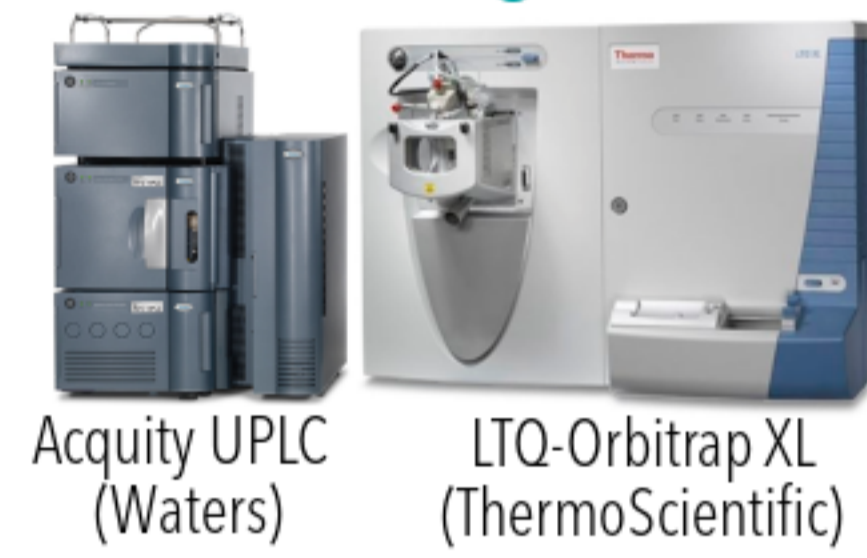
Add appropriate cofactors to activate enzymes (UDPGT, ST, SAM, GST, CYP450, NAT...)

Add the molecule mix

Incubate 3h at 37°C

Metabolites with the same mass difference signature (Twin Peaks approach!)

A technological tool to monitor the native/deuterated mass difference



Preprocessing: peak picking with Wm + incubation control filtering

Explore putative network  
drag nodes to create publication-ready figures

Upload masses, select compound of interest and set mass matching tolerance

CHAMP

Load a list of compound masses (ideally from twin-peaks analysis) and explore putative degradation or metabolization routes, using a mass difference network rooted toward a mass of interest.

Filtered masses

Mass of compound of interest

ppm:

Advanced settings

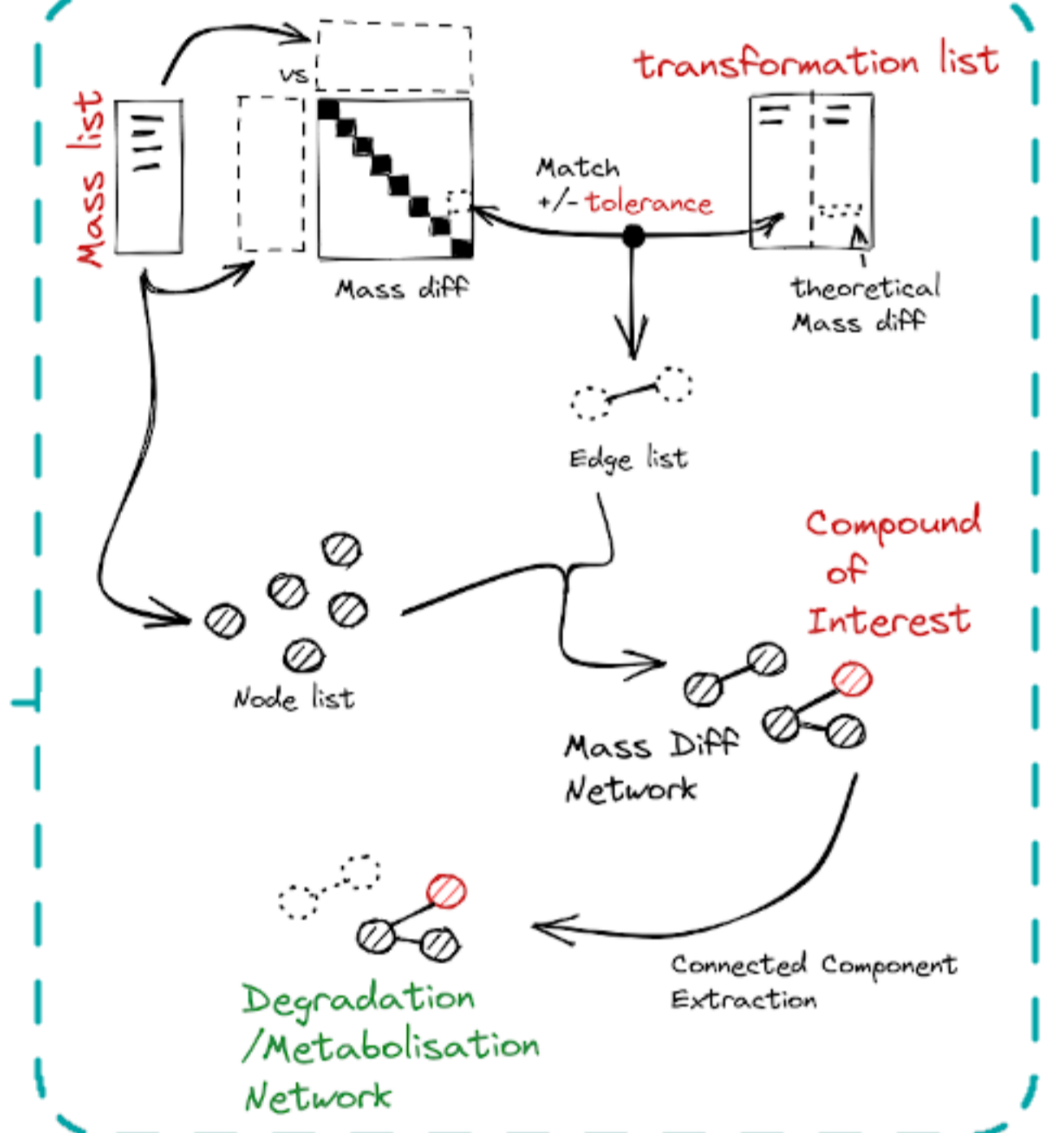
Upload custom transitions

Network Table

Transformation	formula	Theoretical mass shift	mass #1	mass #2	mass shift	Connected to compound of interest
Sulfurylation (+SO3)	SO3	79.95681456	152.07	232.0265	79.9565	true
Uronate (C6H8O6)	C6H8O6	176.032088	152.07	328.1027	176.0327	true
Hydroxylation (+O)	O	15.99491462	152.07	168.0655	15.9955	true
CSH_Conjugation_1	C10H15N3O6S	305.068616	152.07	457.1377	305.0677	true
Cysteine_Conjugation_1 (-H)	C3H6NO2S	119.0041	152.07	271.0747	119.0047	true
Thiolation (+S)	S	31.97207073	152.07	184.0405	31.9705	true

3 See biotransformations, select relevant ones

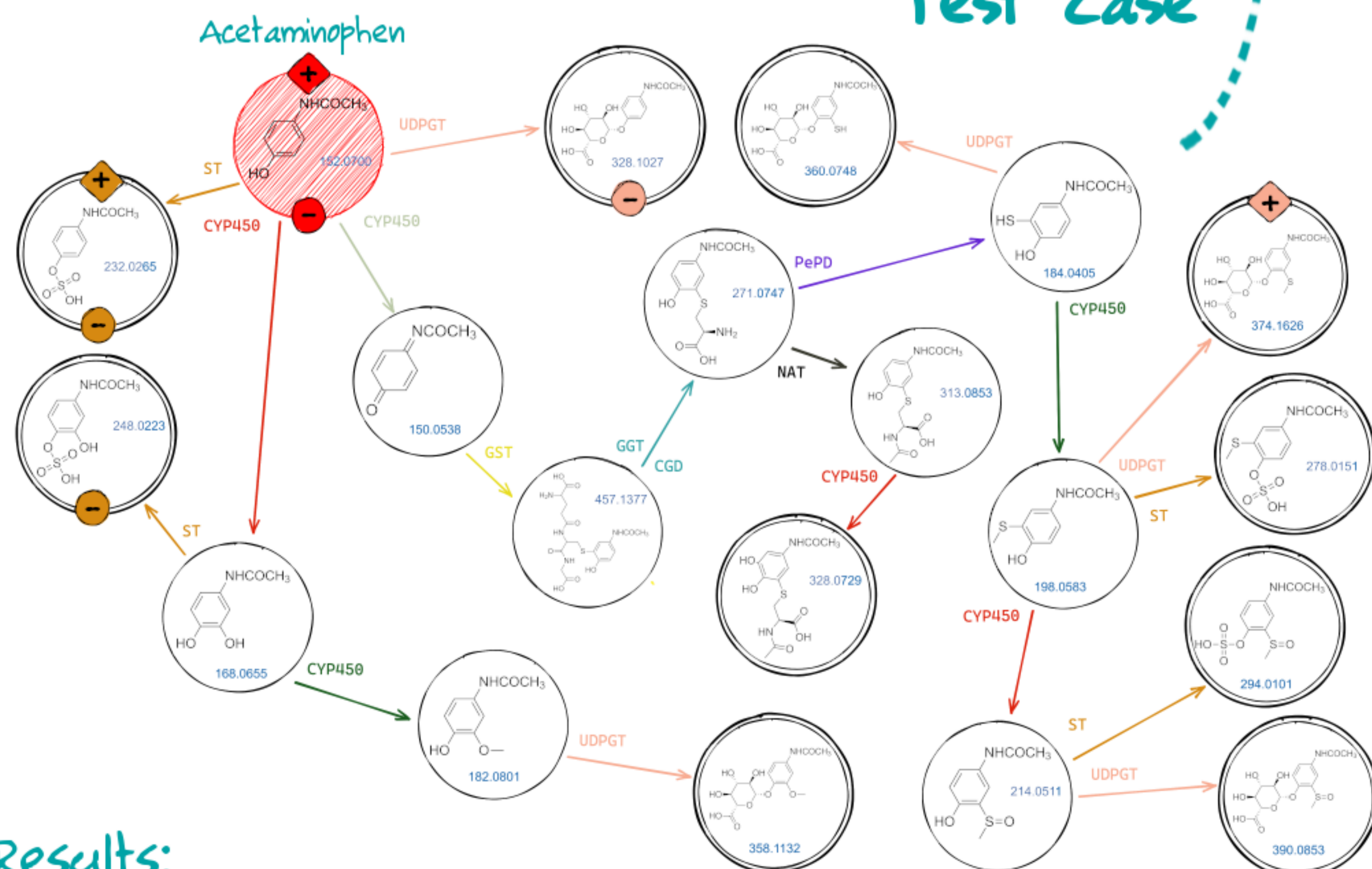
Behind the curtain:



Going further: check for missing links, add custom transitions to fill the gaps

https://champ.sk8.inrae.fr

Test Case



Results:

Acetaminophen's terminal products have been retrieved from Twin Peaks Analysis (⊖ ⊕), and main detoxification routes have been identified using mass difference network\*.

## DISCUSSION / CONCLUSION

- Test case: CHaMP proved to be a very efficient tool for retrieving and reconstructing acetaminophen metabolic pathways from a mass list using a combination of experimental data and knowledge from literature†.

- Higher concentration of acetaminophen mix could bring some routes to saturation (phase II pathways) and yield more terminal nodes (such as phase I products) from experimental data.
- Kinetic experiments could help detect intermediate compounds from experimental data.

- CHaMP's visual and interactive approach made more efficient the reconstruction process of biotransformation pathways from mass data.

## Challenges

- A few missing links remaining due to specific mass shifts, which can be added manually.
- Less relevant alternative routes require manual pruning.

## Perspectives

- Inference of missing intermediates using Steiner Tree pruning.
- Organic pollutants whose metabolic pathways are yet partly unknown are currently being investigated using CHaMP.

\* C. Al-Ayoubi, et al. Metabolism of versicolorin A, a genotoxic precursor of aflatoxin B1: Characterization of metabolites using in vitro production of standards. Food and Chemical Toxicology, 2022  
† J. Keller, et al. "Twin peaks": searching for 4-hydroxynonenal urinary metabolites after oral administration in rats. Redox Biol., 2015  
‡ A. David, et al. Acetaminophen metabolism revisited using non-targeted analyses: Implications for human biomonitoring. Environment International, 2021  
\* T. Naake, A. R. Fernie. MetNet: metabolite network prediction from high-resolution mass spectrometry data in R aiding metabolite annotation. Analytical chemistry, 2018