An extension of over-representation methods based on metabolic distance: application to the interpretation of metabolic perturbation in toxicology

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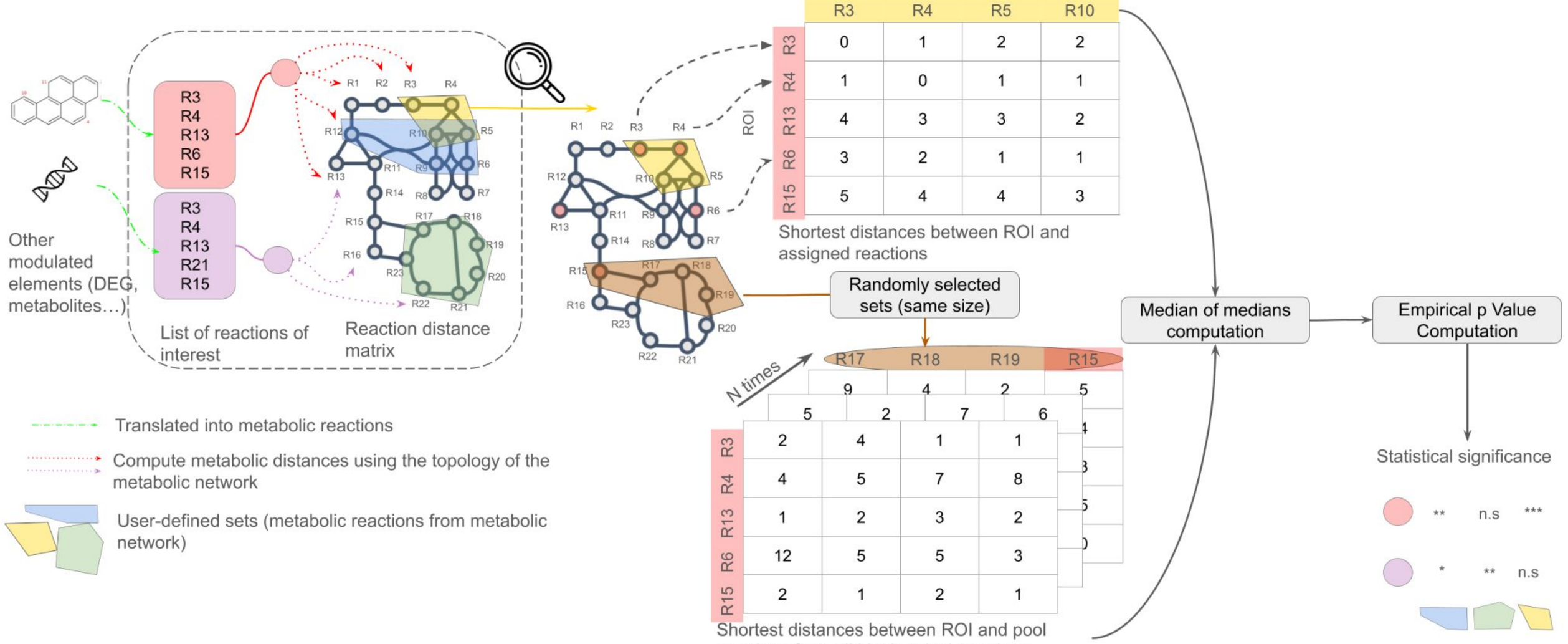
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Context

ORA is a statistical method that determines whether entities from predefined functional categories appear more frequently in a user-defined list of significant features than expected by chance [1]. However, these categories are often poorly suited to infer toxicity pathways. These pathways are key events and represent empirically observable steps leading to biological markers [2]. Moreover, ORA only considers entities within predefined biological groups, which may lead to information loss for entities outside these groups. We therefore propose an alternative approach designed to overcome this limitation.

Alternative method to ORA: using metabolic distance rather than occurrence in set



Toxicology application: Pathways of hepatotoxicity

Allopurinol - Highest (R1, R2, …, R97)

Allopurinol - High (R1, R2, …, R15)

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Valproate - Lowest

Sets of reactions modulated under exposure to 9 chemicals to 5 different doses

Distance based method

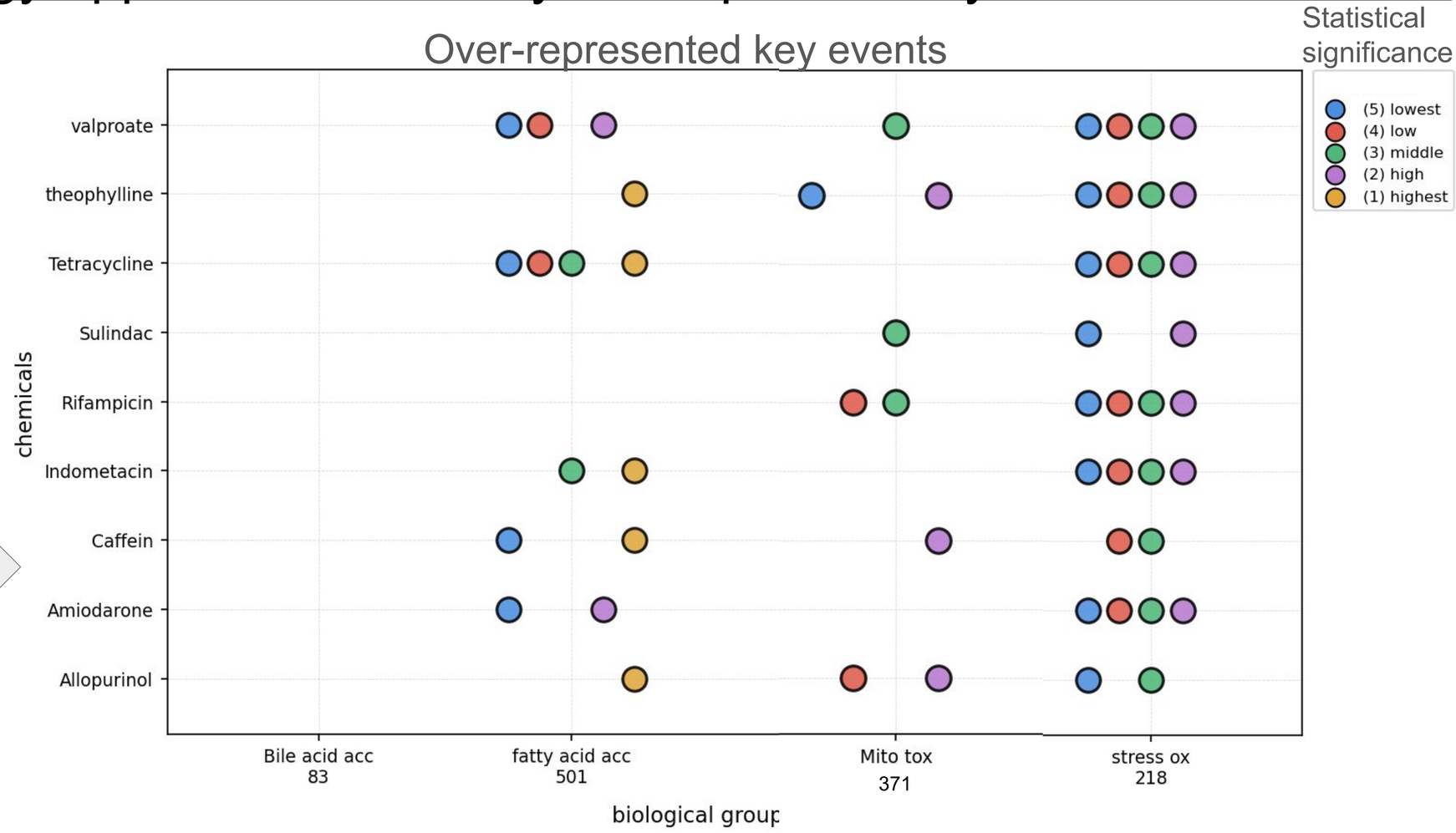
Bile Acid Accumulation (83 reactions)

Fatty Acid Accumulation (501 reactions)

Mitochondrial toxicity (371 reactions)

Oxydative Stress (218 reactions)

Sets of reactions manually associated to toxicity pathways = Key Events [3]



- Bile acid accumulation group is never enriched → Reactions characterizing the Bile Acid Acc. group are not sufficiently specific, resulting in sparse intra group distances.
- Comparing accuracy predictions with literature: **75%** of correct prediction for Valproate, Theophylline and Amiodarone and up to **100%** for Rifampicin.
- Distance-based methods overcome the limitation of relying solely on entity presence in the group by introducing a proximity metric → allows us to use manually defined biological group of interest

References

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[2] Julien E et al; The Key Events Dose-Response Framework: a cross-disciplinary mode-of-action based approach to examining dose-response and thresholds. Crit Rev Food Sci Nutr. 2009
[3] Arnesdotter et al, . Derivation, characterisation and analysis of an adverse outcome pathway network for human hepatotoxicity. Toxicology. 2021