Identifying Drug Repositioning Candidates using Comparative Mechanism Enrichment in Neurodegenerative Diseases

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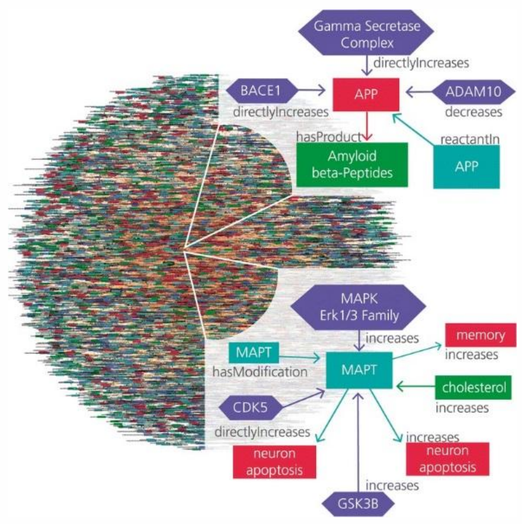
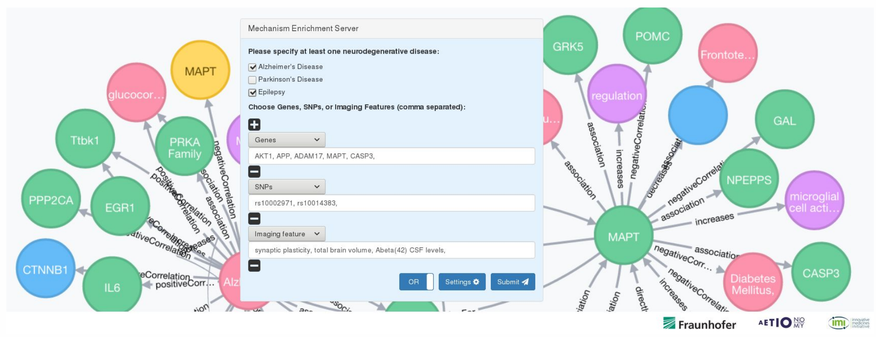
Capturing the Knowledge in Neurological Disorders

We have captured the disease-specific knowledge around Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy in Biological Expression Language (BEL) to represent multiple scales of their pathophysiologies, from the genetic to the phenotypic level.



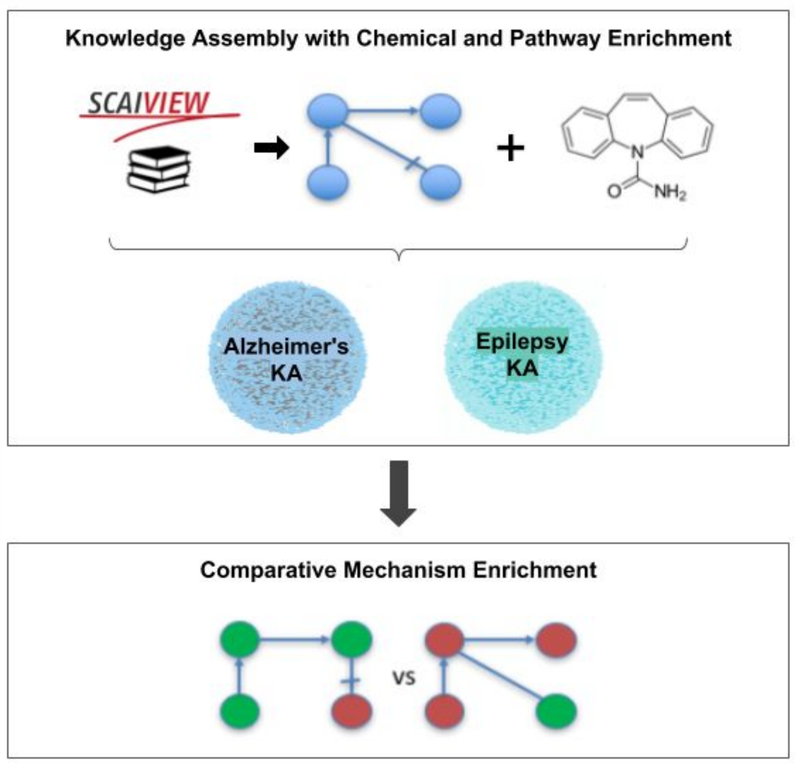
NeuroMMSig - a Web Application for Mechanism Enrichment



We have generated an inventory of candidate mechanisms for each disease into which we categorized the triplets in each knowledge assembly. The inventory is exposed via NeuroMMSig, a web application that supports multi-modal (e.g., genes, variants, and imaging features) mechanism enrichment [1].

Identifying Shared Mechanisms between Comorbidities

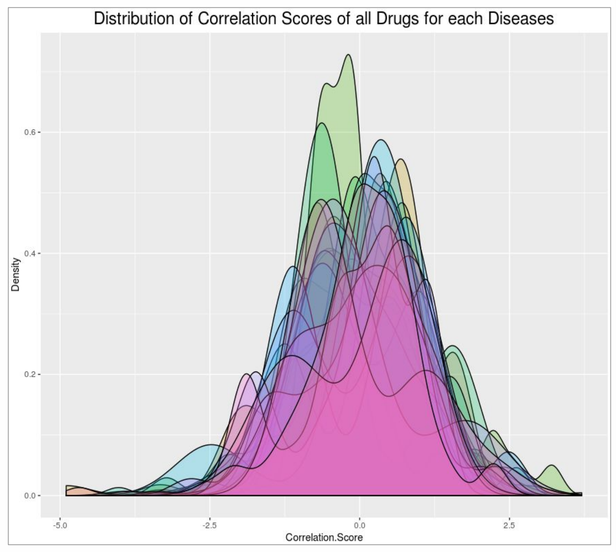
Comparative mechanism enrichment with NeuroMMSig was used to propose the shared mechanisms through which carbamazepine, an antiepileptic drug, might have therapeutic effects in the context of AD [2].



Identifying Drug Repurposing Candidates that Revert Disease Pathway Signatures

As an approach for identifying drug repurposing candidates, we proposed an integrative workflow, *MSDRP*, in which we used multi-omics data (e.g., genetics and transcriptomics data) to investigate how instead of a single target, drugs could modulate a constellation of targets or even entire mechanisms [3].

Our approach leverages pathway enrichment methods to calculate the anti-correlation between the downstream effects of a given drug and the dysregulation observed in the disease context.



Conclusion and Future Work

Using the methods presented in this poster, we have demonstrated how it is possible to identify mechanisms of actions of drugs as well as to propose novel and drug repurposing candidates. Furthermore, the availability of the methods as reusable Python and R packages enable them to be interchanged used with other drug discovery approaches and be run with numerous datasets.

In the future, we aim to systematically validate our results coming from canonical pathway databases with each of our disease-specific knowledge assemblies in NeuroMMSig.

Reproducibility and Resources

Resource	Link
NeuroMMSig	*https://neurommsig.scai.fraunhofer.de*
Shared Mechanisms Analysis	*https://github.com/neurommsig-epilepsy/epicom*
Pathway Analysis	*https://compath.scai.fraunhofer.de* *https://pathme.scai.fraunhofer.de*
MSDRP	*https://github.com/asifemon/msdrp*

References

[1] Domingo-Fernández, D. *et al*. (2017). Multimodal Mechanistic Signatures for Neurodegenerative Diseases (NeuroMMSig): a web server for mechanism enrichment. *Bioinformatics*, 33(22), 3679-3681.
[2] Hoyt, C. T. and Domingo-Fernández, D., *et al.* (2018). A systematic approach for identifying shared mechanisms in epilepsy and its comorbidities. *Database,* bay050.
[3] Emon, M. A., *et al.* (2019). Identification and Prioritization of Drugs Reverting Dysregulated Pathway Signatures as Repurposing Candidates. *In preparation*.

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