

Mechanisms: NeuroMMSig, the mechanism-enrichment server

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AETIONOMY Final Symposium
Bonn
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innovative
medicines
initiative

Mission

To increase knowledge of the causes of Alzheimer´s and Parkinson´s Disease by generating a mechanism-based taxonomy; to validate the taxonomy in a prospective clinical study that demonstrates its suitability for identifying patient subgroups (based on discrete disease mechanisms); to support future drug development and lay the foundation for improved identification and treatment of patient subgroups currently classified as having AD or PD.



AETIONOMY

Organising Knowledge about Neurodegenerative Disease Mechanisms for the Improvement of Drug Development and Therapy



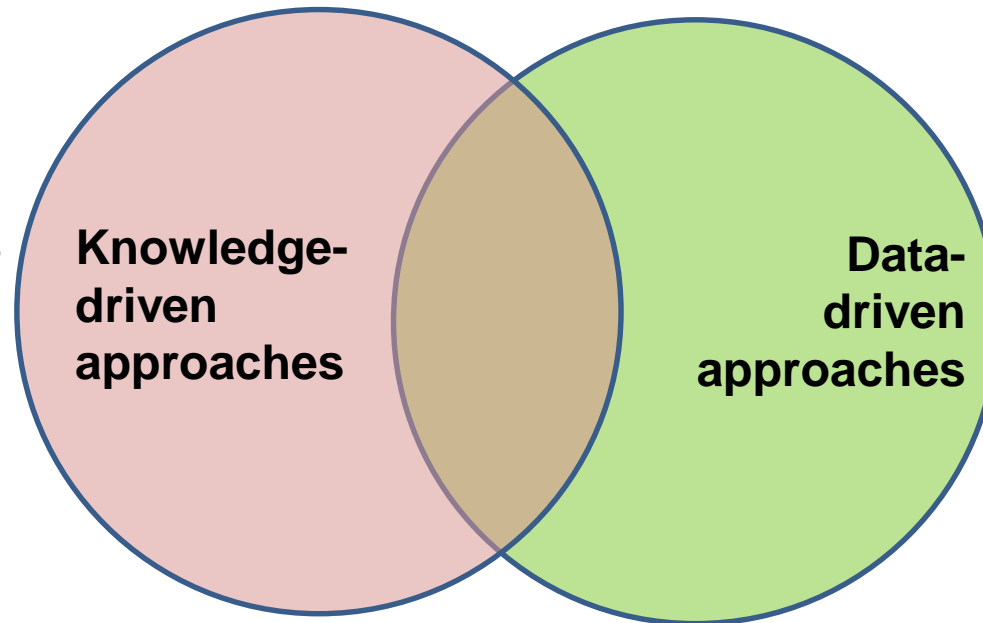


AETIONOMY

Organising Knowledge about Neurodegenerative Disease Mechanisms for the Improvement of Drug Development and Therapy



- AETIONOMY KB
- **NeuroMMSig**
- Data Catalogue
- ...



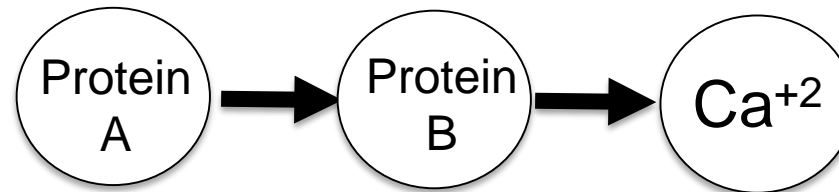
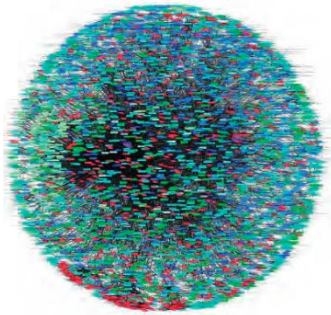
- Clustering
- Bayesian
- Longitudinal modeling
- tranSMART
- ...



NeuroMMSig*

*Domingo-Fernández, D., *et al.* "Multimodal Mechanistic Signatures for Neurodegenerative Diseases (NeuroMMSig): a web server for mechanism enrichment." *Bioinformatics* (2017).

Capturing the disease-specific knowledge from literature

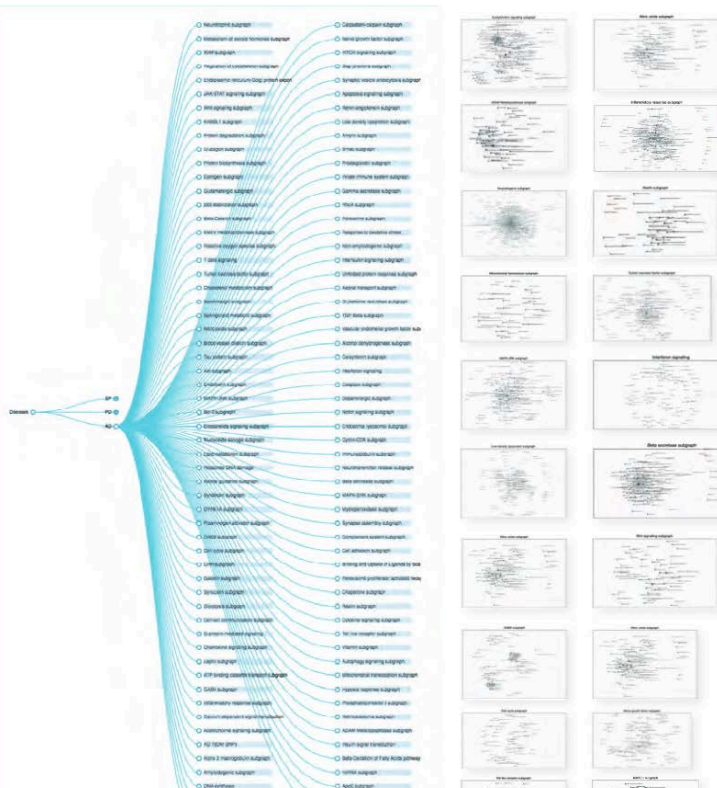
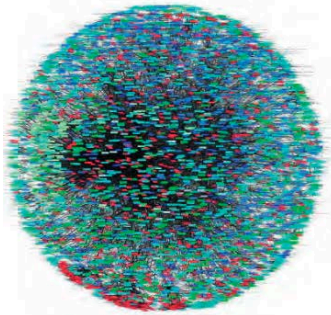


“[Protein A] increases [Protein B] leading to an increase in [Ca⁺²]”

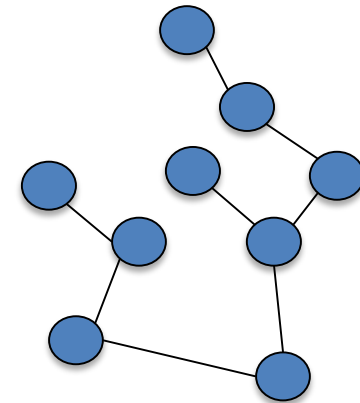


NeuroMMSig

Capturing the disease-specific knowledge from literature



Classifying each relation in the network into the mechanism(s) they participate

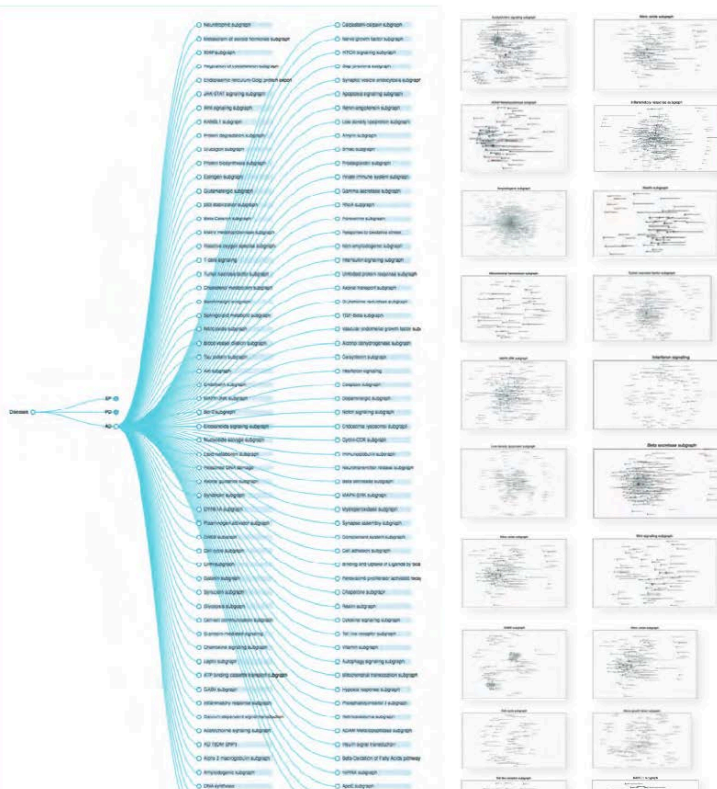
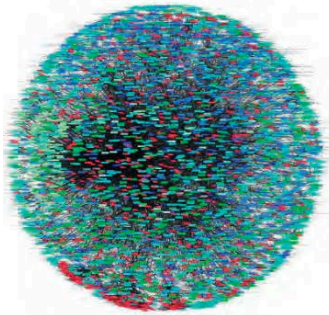


“[Protein A] leads to the generation of amyloid plaques”

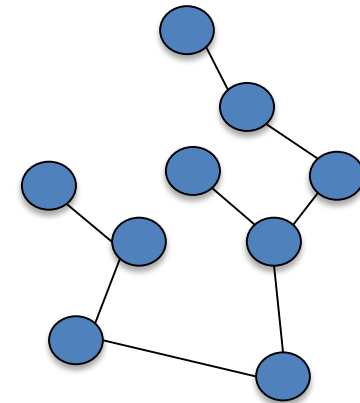


NeuroMMSig

Capturing the disease-specific knowledge from literature



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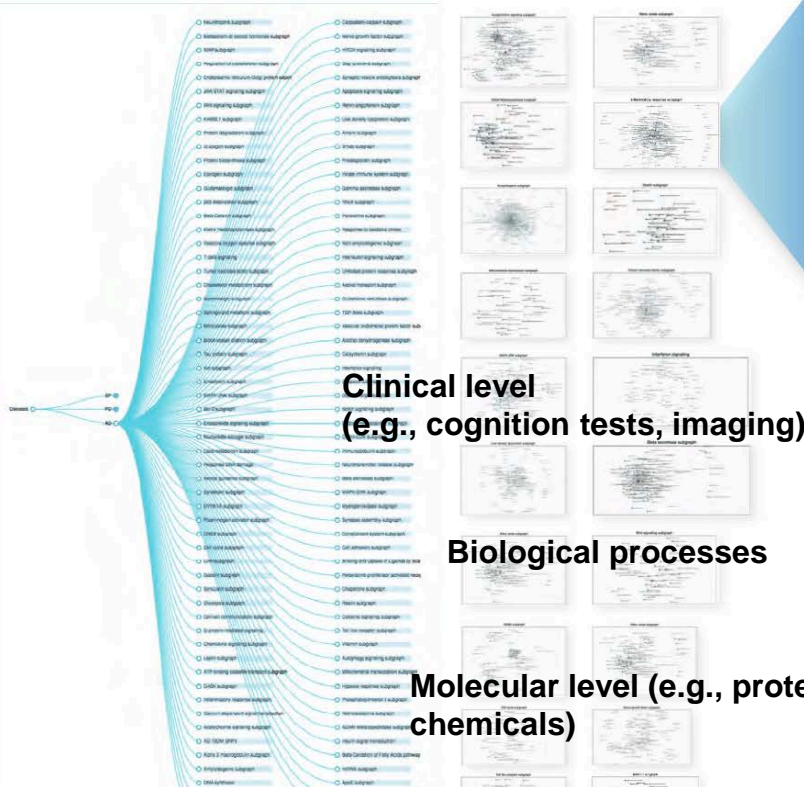
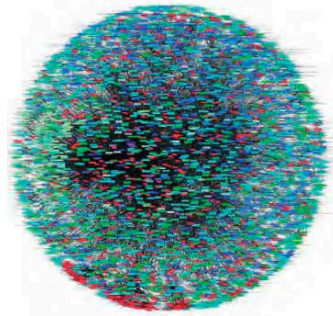
Amyloid cascade network



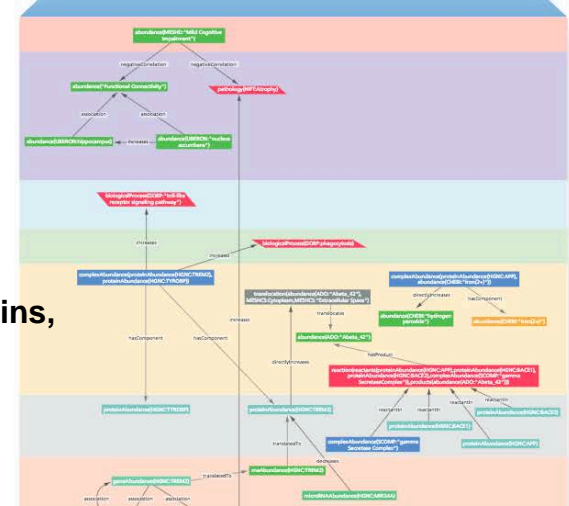
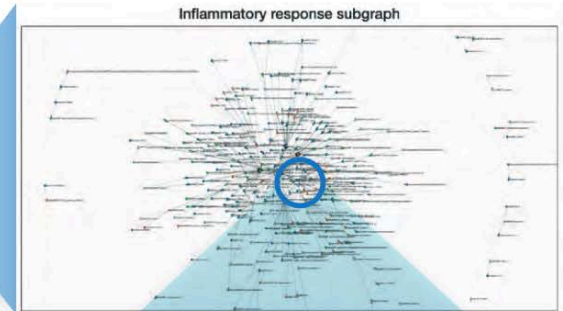
NeuroMMSig

Neuroinflammation mechanistic subgraph representing multiple biological levels

Capturing the disease-specific knowledge from literature



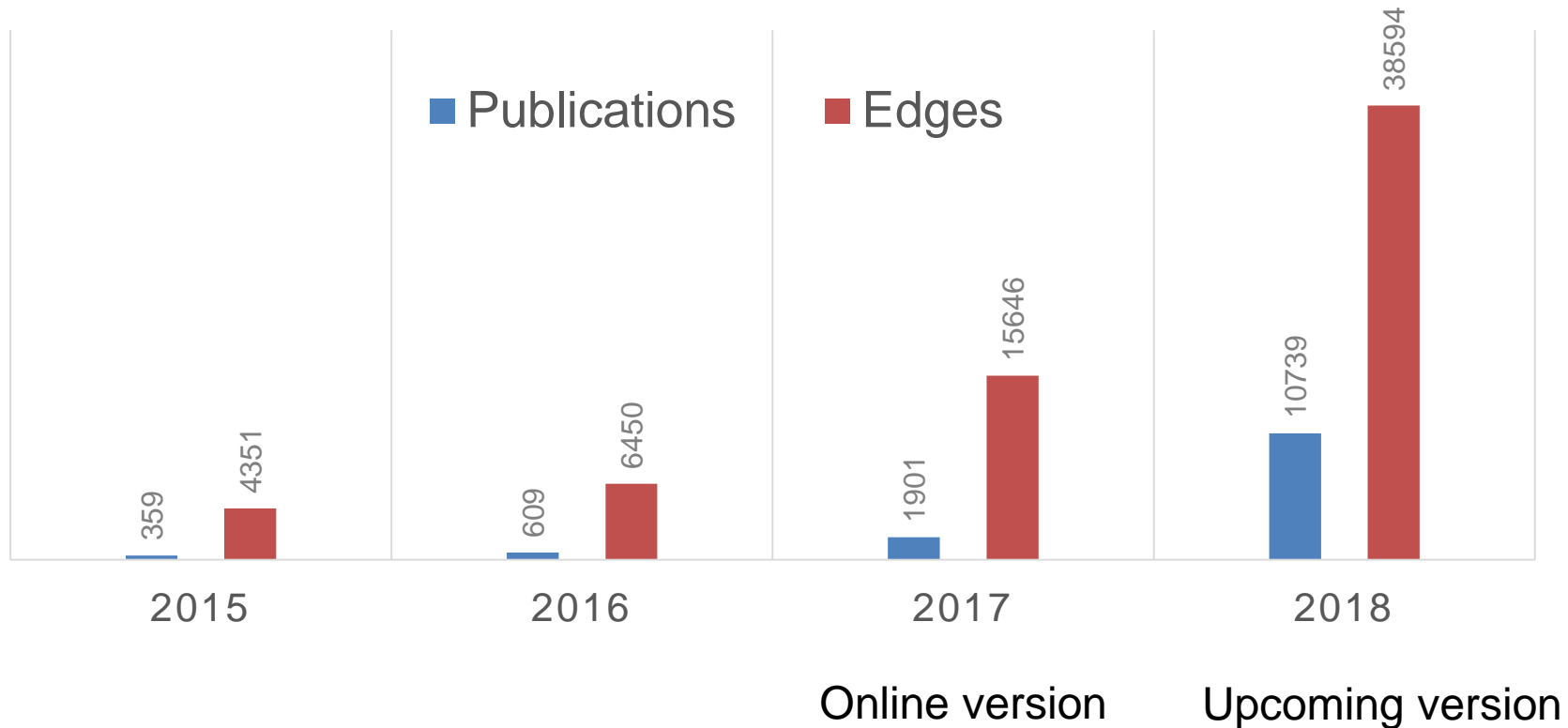
Classifying each relation in the network into the mechanism(s) they participate





Growth during the project

NEUROMMSIG AD





NeuroMMSig – Web application

NeuroMMSig Quick Tour ▾ About NeuroMMSig Imprint

Admin

Mechanism Enrichment Server

Please specify at least one neurodegenerative disease:

- Alzheimer's Disease
- Parkinson's Disease
- Epilepsy

Choose Genes, SNPs, or Imaging Features (comma separated):

+ Genes: APP, MAPT, A2M,

- SNPs: rs10002971, rs10014383, rs143345034,

- Imaging feature: Brain atrophy, amyloid deposition CSF,

-

OR Settings Submit

<https://neurommsig.scai.fraunhofer.de/>





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Genes
-

SNPs
-

Imaging feature
-

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Admin

The screenshot shows the 'Mechanism Enrichment Server' interface. It includes a dropdown menu for 'Please specify at least one neurodegenerative disease:' with options for Alzheimer's Disease (checked), Parkinson's Disease, and Epilepsy. Below this is a section for 'Choose Genes, SNPs, or Imaging Features (comma separated):' with three input fields: 'Genes' containing 'APP, MAPT, A2M,', 'SNPs' containing 'rs10002971, rs10014383, rs143345034,' (highlighted with a black box), and 'Imaging feature' containing 'Brain atrophy, amyloid deposition CSF, |'. There are 'OR', 'Settings', and 'Submit' buttons at the bottom of the form. The background features a network diagram with nodes like POMC, Frontote..., GAL, NPEPPS, microglial cell acti..., CASP3, Diabetes Mellitus, cognition, CASP4, KLC1, MAPT, IL6, CTNNB1, EGR1, PPP2CA, Ttbk1, glucocor..., and saxaglip... connected by various relationship arrows.

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<https://neurommsig.scai.fraunhofer.de/>






NeuroMMSig – Web application

Enriched mechanisms

Subgraph name	Context	Enrichment	Select	Drugs	SNPs	Co-expression network	miRNA			
Akt subgraph	AD	0.36	<input type="checkbox"/>		SNP					
Matrix metalloproteinase subgraph	AD	0.04	<input type="checkbox"/>		SNP					
Nerve growth factor subgraph	AD	0.03	<input type="checkbox"/>		SNP					

Visualize Network
Download Excel 

<https://neurommsig.scai.fraunhofer.de/>

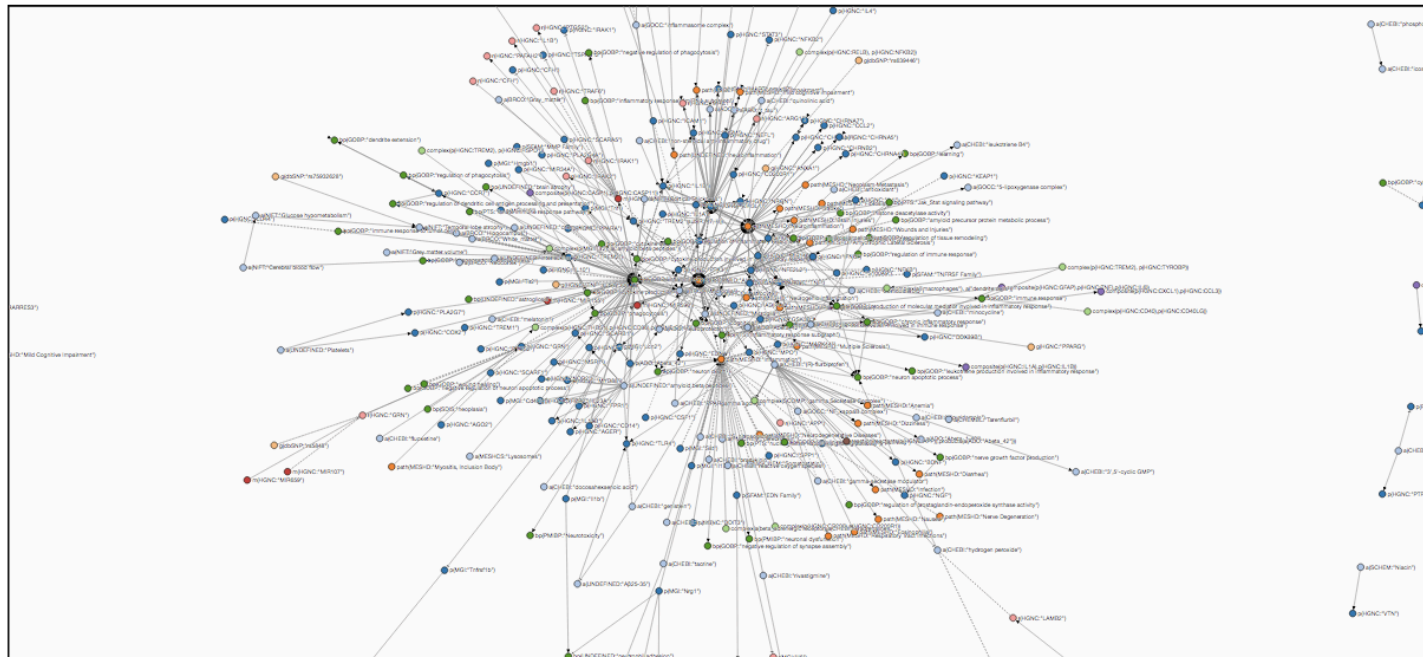




NeuroMMSig – Web application

NODES ▾ EDGES ▾ BIOLOGICAL PROCESSES ▾ CANDIDATE MECHANISMS ▾ FUNCTIONALITIES ▾ EXPORT GRAPH ▾ LEGEND

Inflammatory response subgraph



<https://neurommsig.scai.fraunhofer.de/>





NeuroMMSig – Overview

- Comprises a candidate mechanism collection from three of the major neurological disorders
 - Alzheimer's (126), Parkinson's (76), and epilepsy (31)





NeuroMMSig – Overview

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 - Alzheimer's (126), Parkinson's (76), and epilepsy (31)
- High resolution, disease-specific pathophysiology graphs
 - Opposite to generalistic pathway databases such as KEGG and Reactome*

*Domingo-Fernandez, D., *et al.* (2018). ComPath: An ecosystem for exploring, analyzing, and curating mappings across pathway databases. *Nature Systems Biology and Applications*. In press

*Domingo-Fernandez, D., *et al.* (2018). PathMe: Merging and exploring mechanistic pathway knowledge. *bioRxiv*, 451625.





NeuroMMSig – Overview

- Comprises a candidate mechanism collection from three of the major neurological disorders
 - Alzheimer's (126), Parkinson's (76), and epilepsy (31)
- High resolution, disease-specific pathophysiology graphs
 - Opposite to generalistic pathway databases such as KEGG and Reactome*
- Candidate mechanisms are computable networks
 - Data can be used to contextualize hypotheses
 - Algorithmic and query functionalities built-in



NeuroMMSig - Algorithmics

- NeuroMMSig enrichment algorithm
 - Retrieves the mechanisms related to a given molecular or phenotypic signature
- Reverse Causal Reasoning (RCR)
 - Test and challenge the concordance between knowledge (what we know) and experimental results (patterns found)
- Heat diffusion
 - Quantifies the perturbation of differentially expressed molecular entities in a cause-and-effect model
- "Story" finder
 - Path mining queries that identify chain of dysregulations between interesting nodes (e.g., ways in which molecular signatures can lead to clinical end-points)

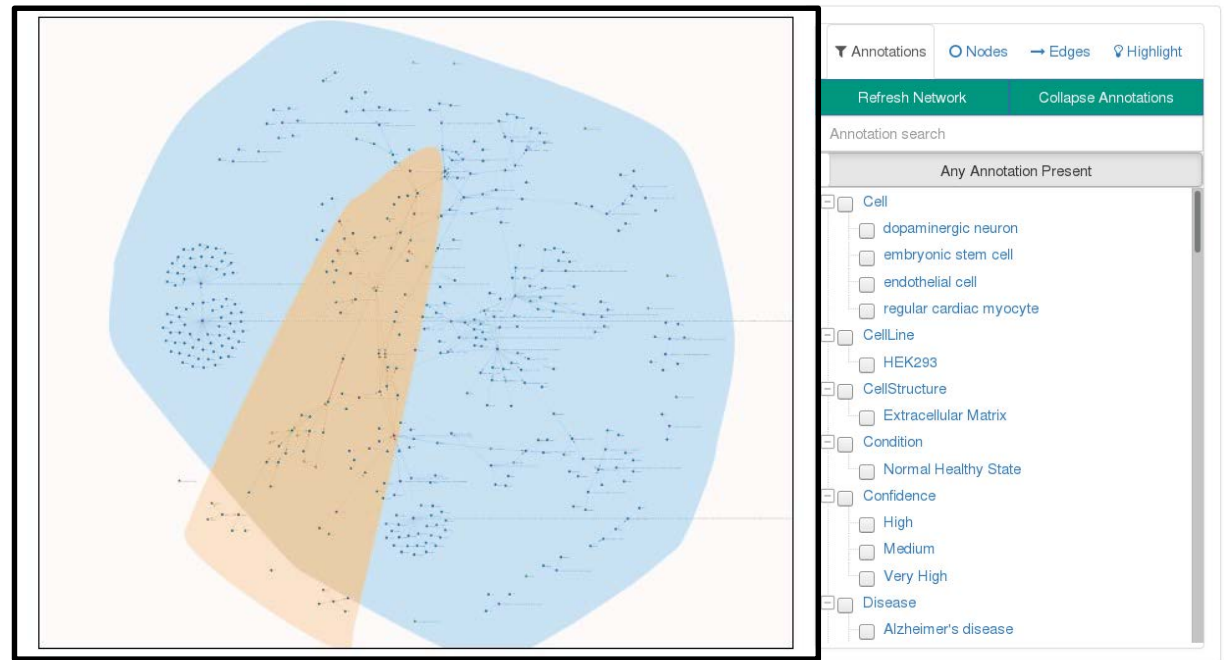


NeuroMMSig - Update

1. Novel visualization
 - Mechanism crosstalk



Crosstalk between two mechanisms

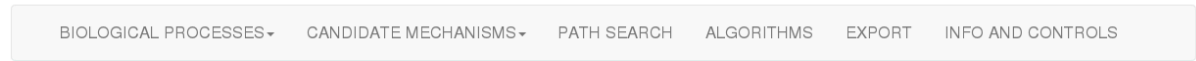




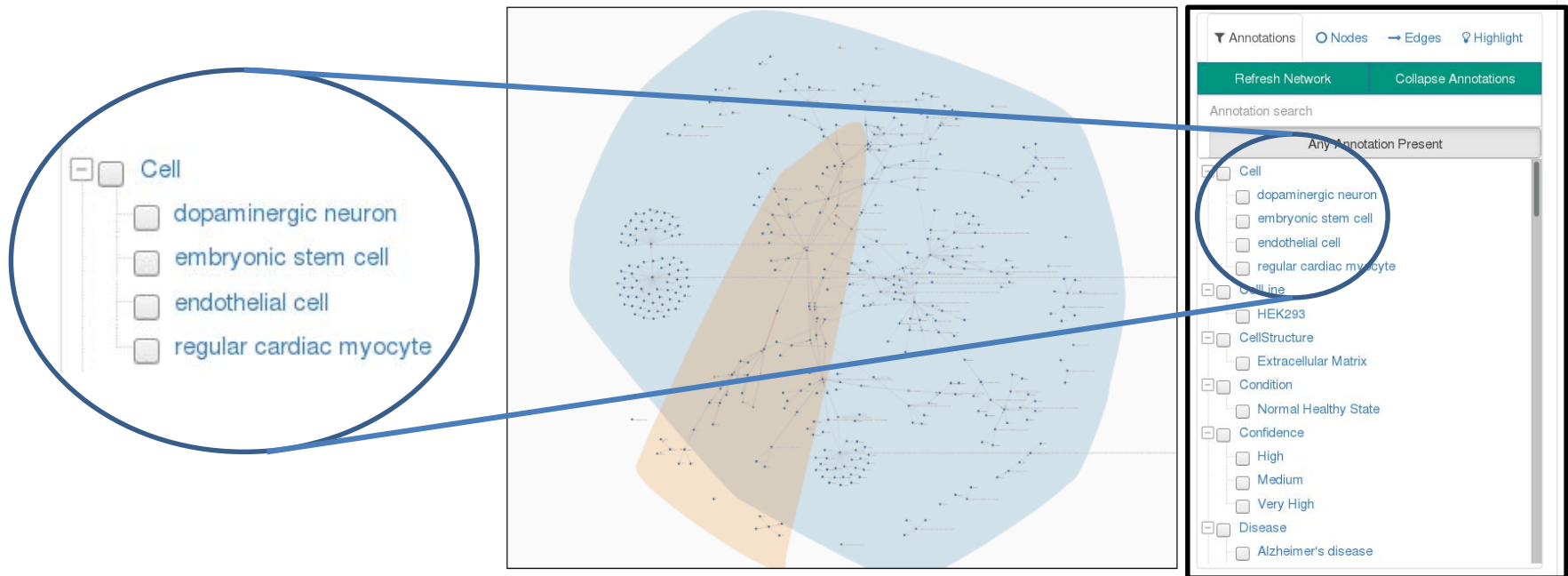
NeuroMMSig - Update

1. Novel visualization

- Mechanism crosstalk
- Network query builder



Crosstalk between two mechanisms





NeuroMMSig - Update

1. Novel visualization
2. Data storage

Summary of Experiments					
Identifier	Query	Permutations	Omic	Name	Description
16	14	250	13	EarlyAD.csv	Patients from GSE28146 with early Alzheimer's disease Delete
17	14	250	14	ModAD.csv	Patients from GSE28146 with moderate Alzheimer's disease Delete
18	14	250	15	SevAD.csv	Patients from GSE28146 with severe Alzheimer's disease Delete

Users can upload and store clinical datasets

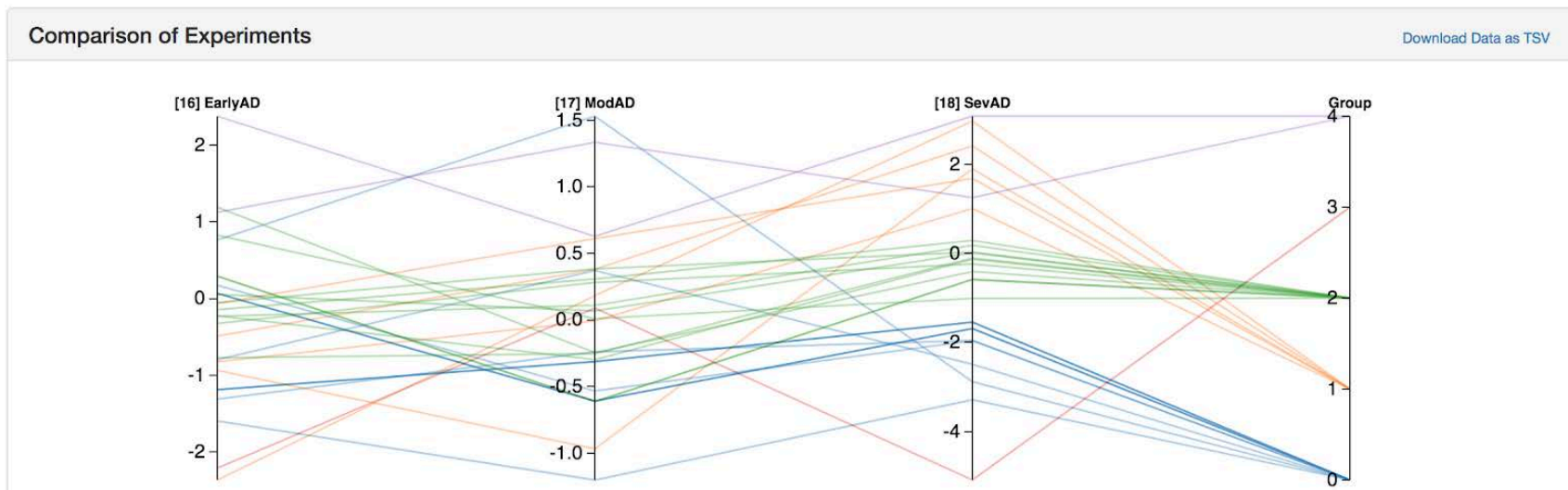




NeuroMMSig - Update

1. Novel visualization
2. Data storage
3. Novel algorithmic implementations for patient stratification*

*Hoyt, C. T., Domingo-Fernández, D, and Hofmann-Apitius, M. (2018). BEL Commons: an environment for exploration and analysis of networks encoded in Biological Expression Language. *Database*. In press

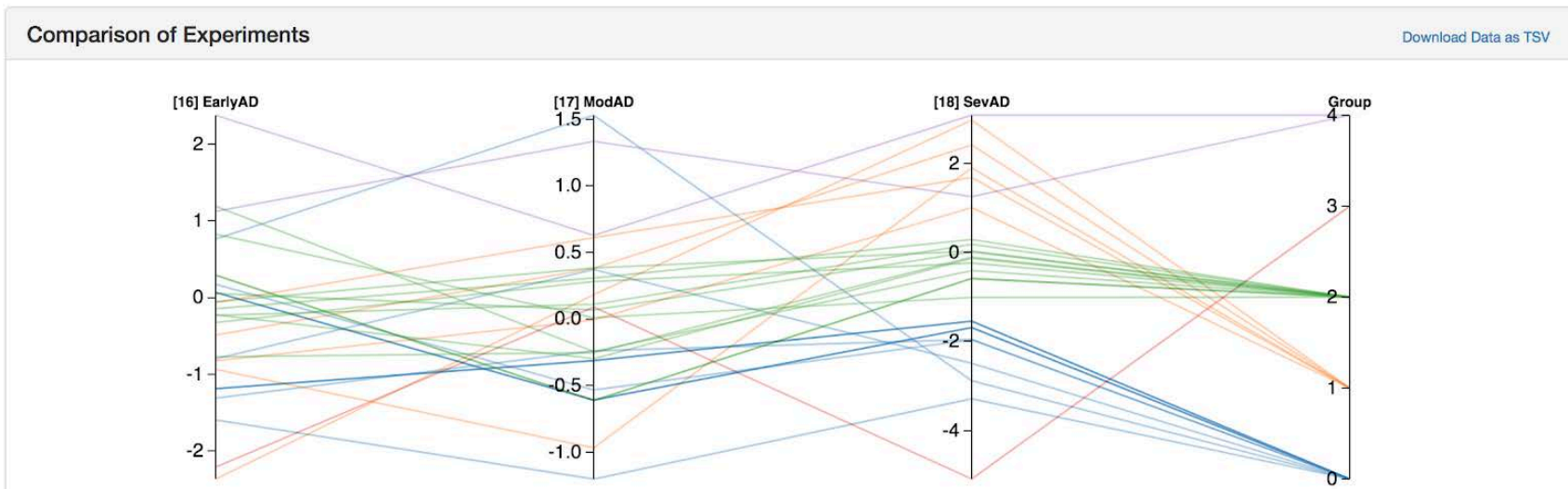


Users can run different algorithms on uploaded data



NeuroMMSig - Update

1. Novel visualization
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3. Novel algorithmic implementations for patient stratification





Ongoing and future work

- Releasing NeuroMMSig 2.0

- New features + case scenario on ADNI/AddNeuroMed





Ongoing and future work

- Releasing NeuroMMSig 2.0

- New features + case scenario on ADNI/AddNeuroMed

- Patient stratification & predictive modeling

- Clustering and machine learning activities* use NeuroMMSig features (UCB, ICM, and Fraunhofer)

Khanna, S.[†], Domingo-Fernandez, D.[†] *et al.* (2018). Using Multi-Scale Genetic, Neuroimaging and Clinical Data for Predicting Alzheimer's Disease and Reconstruction of Relevant Biological Mechanisms. *Scientific reports*, 8(1), 11173.





Ongoing and future work

- Releasing NeuroMMSig 2.0
 - New features + case scenario on ADNI/AddNeuroMed
- Patient stratification & predictive modeling
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- Human Brain Pharmacome project
 - Drug repurposing on Alzheimer's disease





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- Human Brain Pharmacome project
 - Drug repurposing on Alzheimer's disease
- Prediction of novel causal links*
 - Knowledge graph embedding models to predict novel links (UniBonn)

Ali, M., *et al.* (2018). BioKEEN: A library for learning and evaluating biological knowledge graph embeddings. *bioRxiv*. 475202





Conclusion and outlook

- Key message

- NeuroMMSig is the inventory underlying the first draft of a mechanism-based taxonomy for AD and PD

- Legacy

- NeuroMMSig will be maintained and further developed at least until 2023
- Take-up from other EU projects (e.g., PHAGO)
- Further development in the Virtual Brain Cloud project where a priori knowledge constrains brain simulations



Acknowledgements

- Prof. Dr. Martin Hofmann-Apitius
- Prof. Dr. Holger Fröhlich
- Dr. Alpha Tom Kodamullil
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- Asif Mohammed Emon
- Stephan Springstubbe
- All Fraunhofer SCAI Team
- All AETIONOMY partners





Thank you for your attention

Any questions?