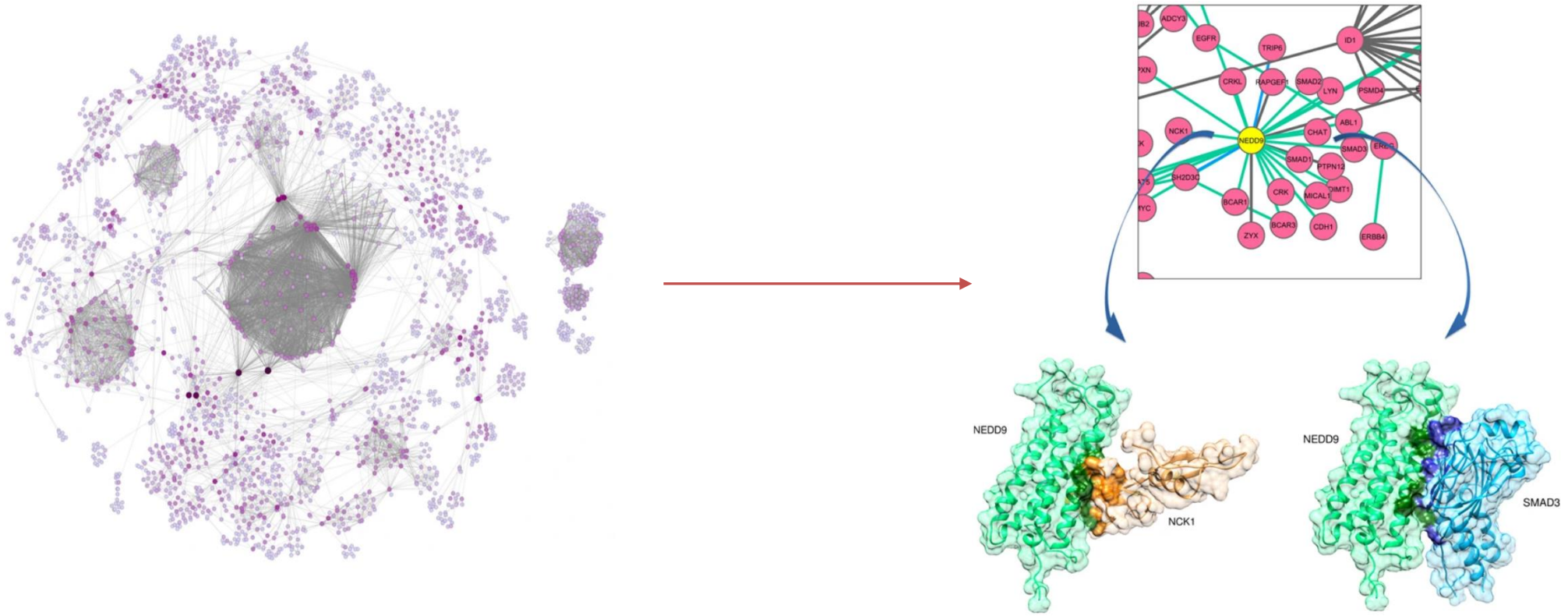
Prediction of the Function of Protein Interactions in Post-Translational Modifications

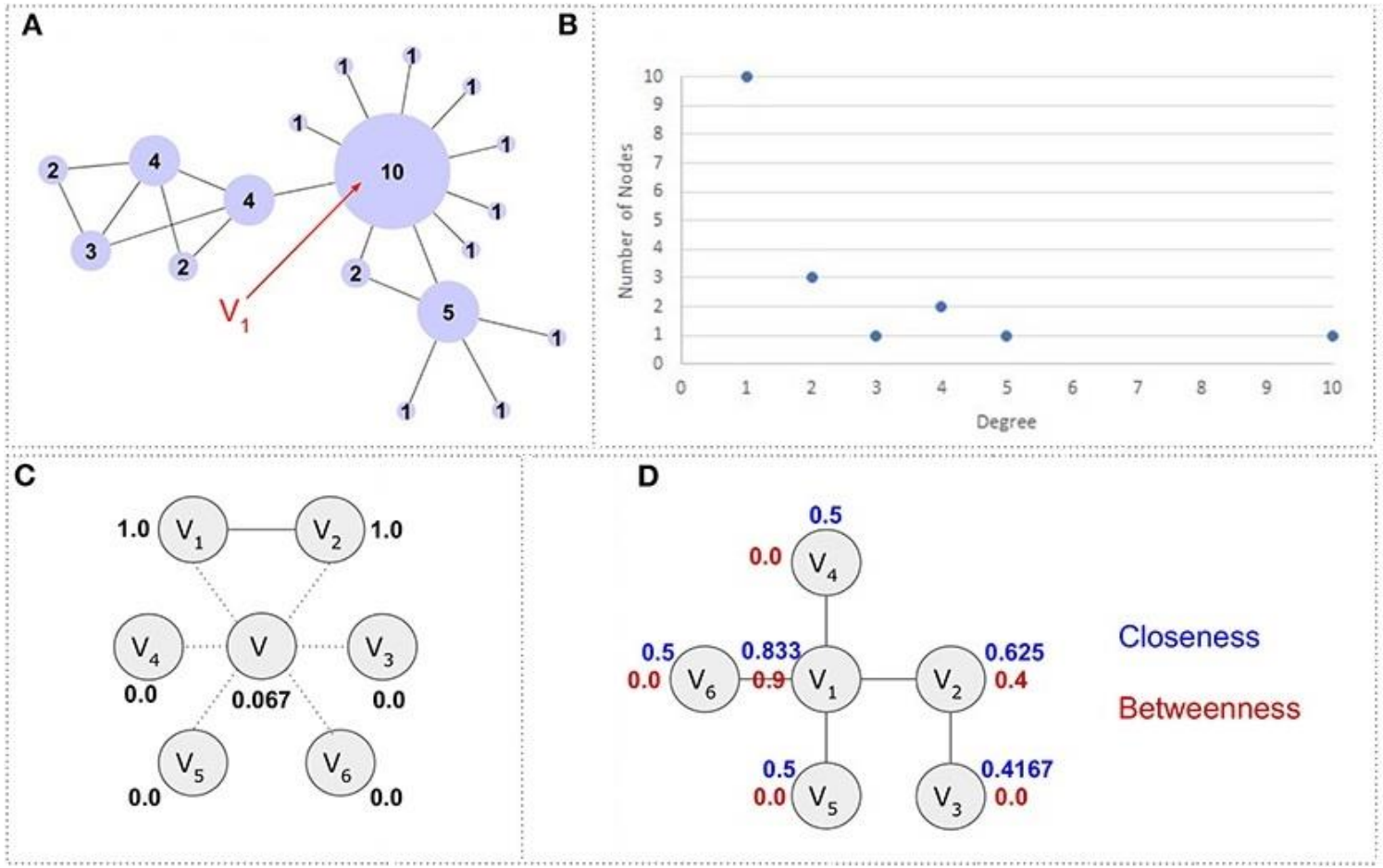
2023 M.Sc. Biology & Biomedicine
Module: Proteinbiochemie und Bioinformatik

Aimilia Christina Vagiona
PhD student
Supervisor: Miguel Andrade

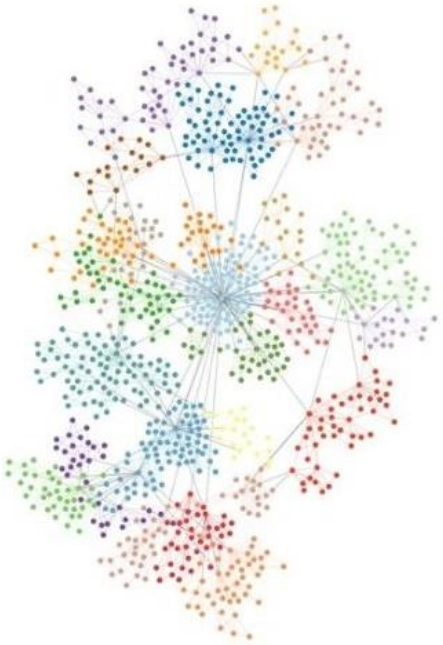
Why do we study the human interactome?



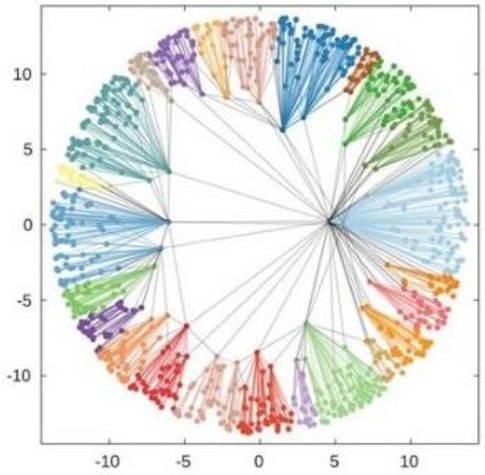
Network theory



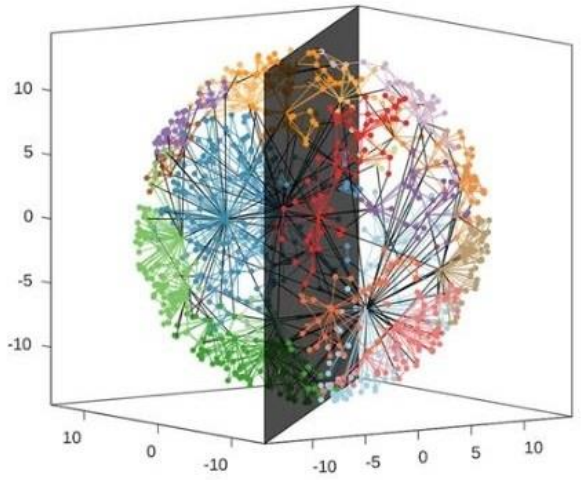
Hyperbolic network model



Euclidean

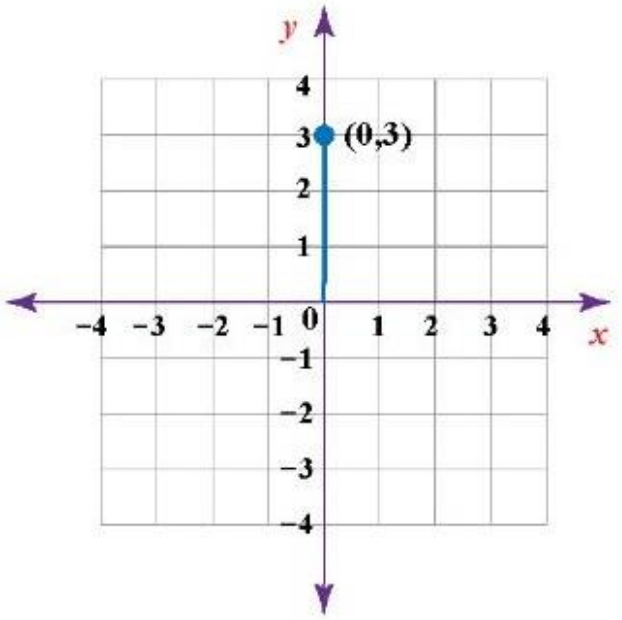


Hyperbolic PS model in 2D

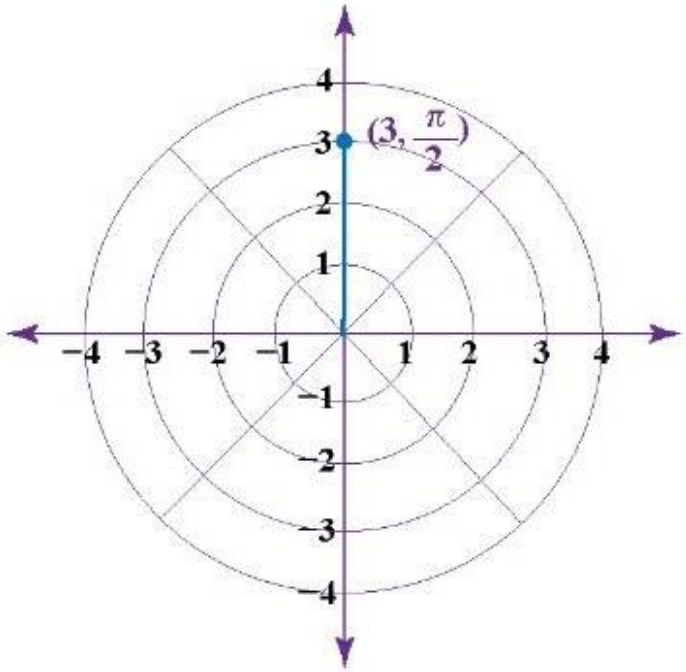


Hyperbolic PS model in 3D

PS model



Euclidean Coordinates (x, y)



Polar Coordinates (r, theta)

1) Node Sorting: Nodes are sorted in decreasing order by degree

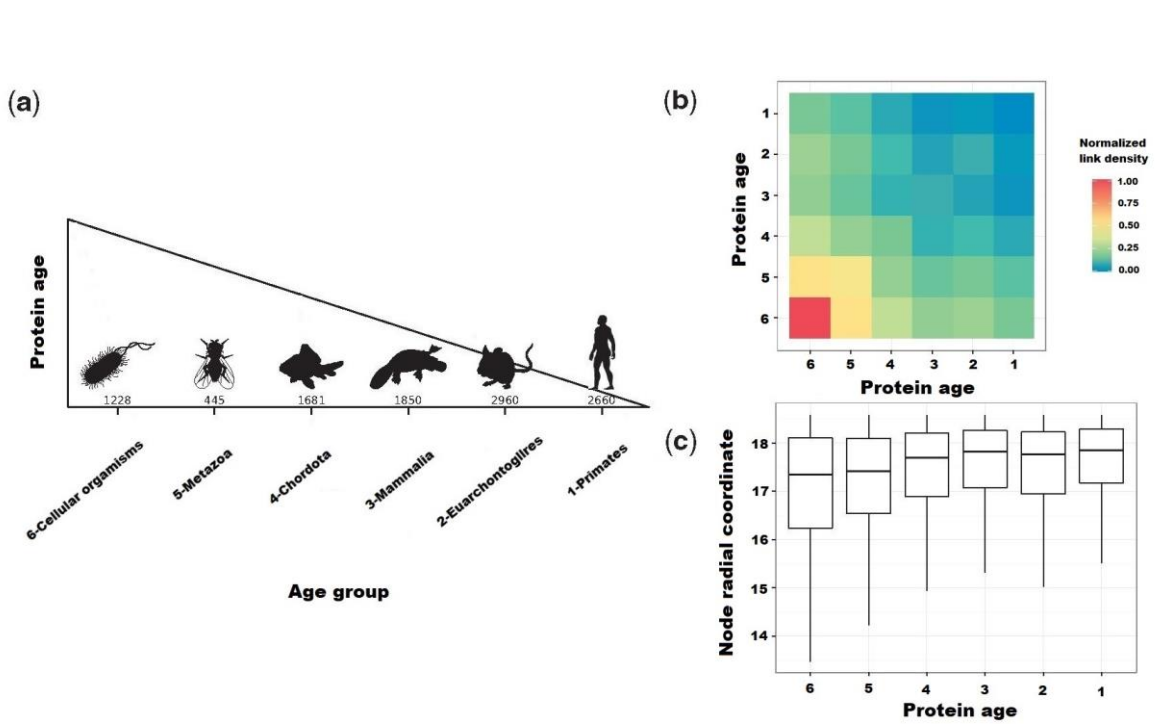
2) Starting Point: The first node is placed at the center and it gets a random angle

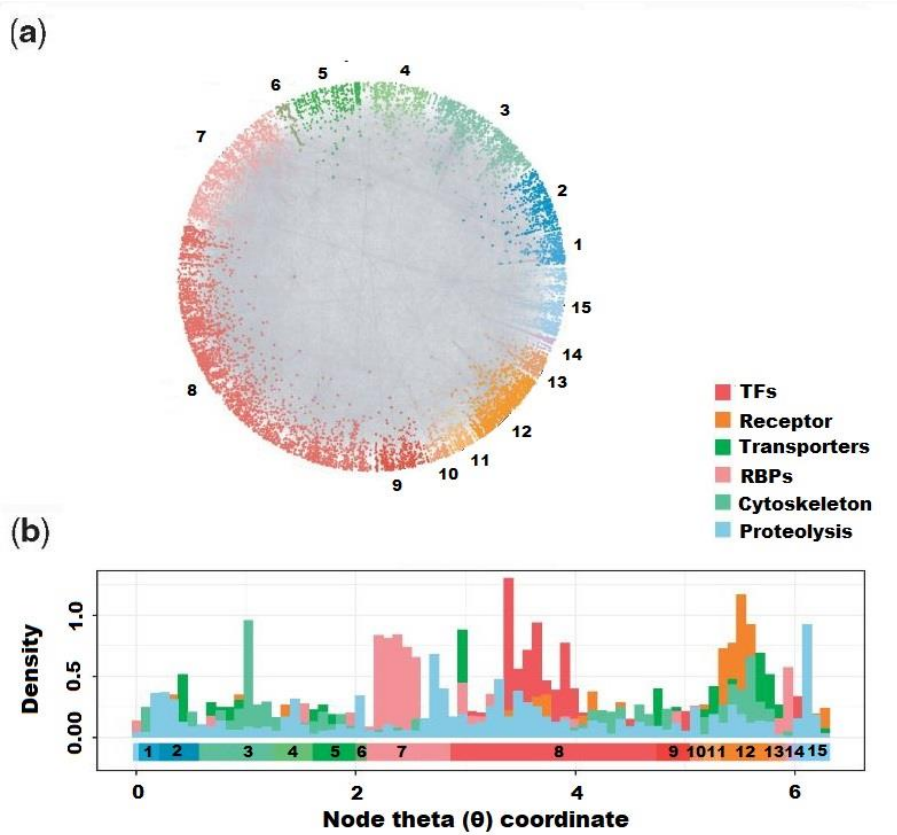
3) Expanding the Space: embedding new nodes:

- Distance from Center: in the new node assigned radial coordinate $r_i = 2\ln i$
- Adjusting Positions: The positions of existing nodes are adjusted based on their distances from the new node ($r_j(i) = \beta\, r_j + (1 - \beta)\, r_i$)
- Finding the Best Angle: The new node is given an anglular coordinate that maximizes the likelihood of the PS model

4) Repeat for All Nodes: Steps 2 and 3 are repeated for every node in the network.

hPIN in the Hyperbolic Space





hPIN in the Hyperbolic Space

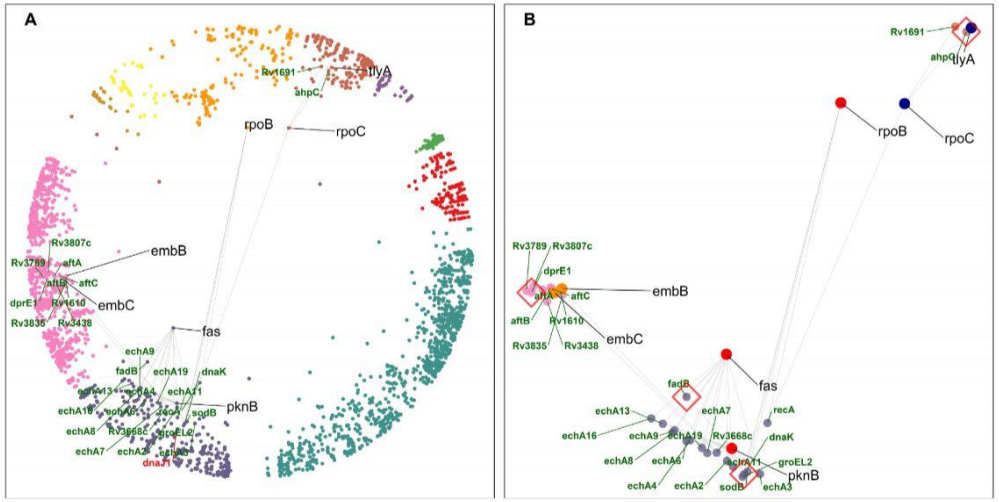
International Journal of *Molecular Sciences*

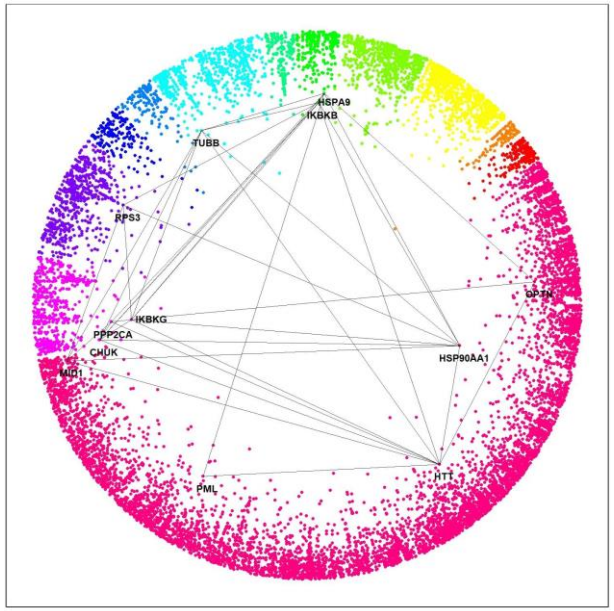
MDPI

Article

Selection of Multi-Drug Targets against Drug-Resistant *Mycobacterium tuberculosis* XDR1219 Using the Hyperbolic Mapping of the Protein Interaction Network

Noor ul Ain Zahra [1,2], Aimilia-Christina Vagiona [2], Reaz Uddin [1,*] and Miguel A. Andrade-Navarro [2,*]





International Journal of *Molecular Sciences*

MDPI

Article

Analysis of Huntington's Disease Modifiers Using the Hyperbolic Mapping of the Protein Interaction Network

Aimilia-Christina Vagiona [1], Pablo Mier [1], Spyros Petrakis [2] and Miguel A. Andrade-Navarro [1,*]

Hyperbolic applications

nature › scientific reports › articles › article

Article | Open access | Published: 06 August 2021

The inherent community structure of hyperbolic networks

Bianka Kovács & Gergely Palla

Scientific Reports **11**, Article number: 16050 (2

nature › nature communications › articles › article

Article | Open access | Published: 05 May 2021

Deep generative model embedding of single-cell RNA-Seq profiles on hyperspheres and hyperbolic spaces

Jiarui Ding & Aviv Regev

Nature Communications **12**, Article number: 2554 (2021) | Cite this article

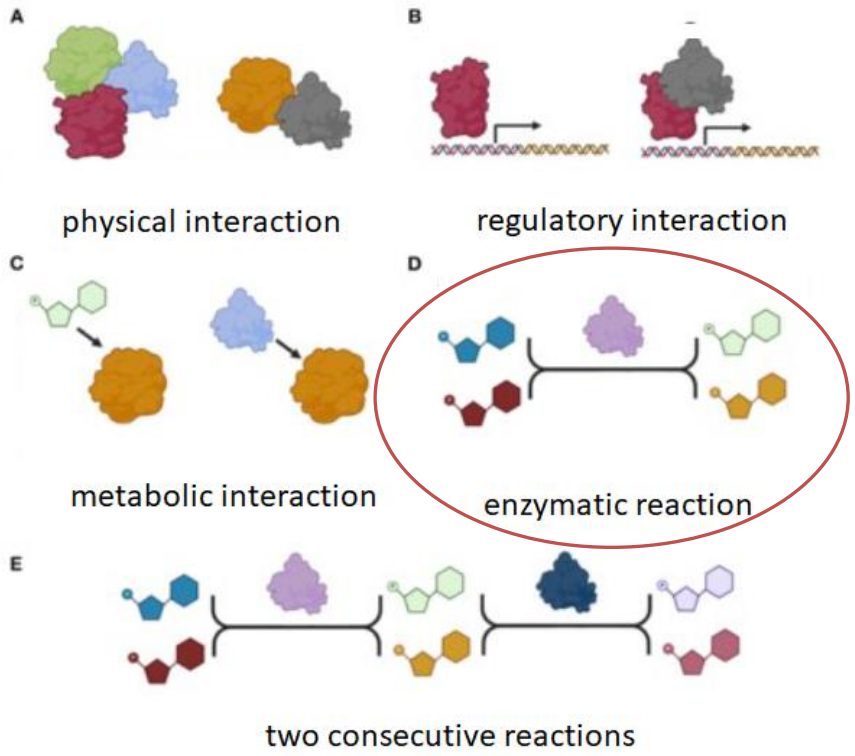
Hyperbolic Deep Neural Networks: A Survey

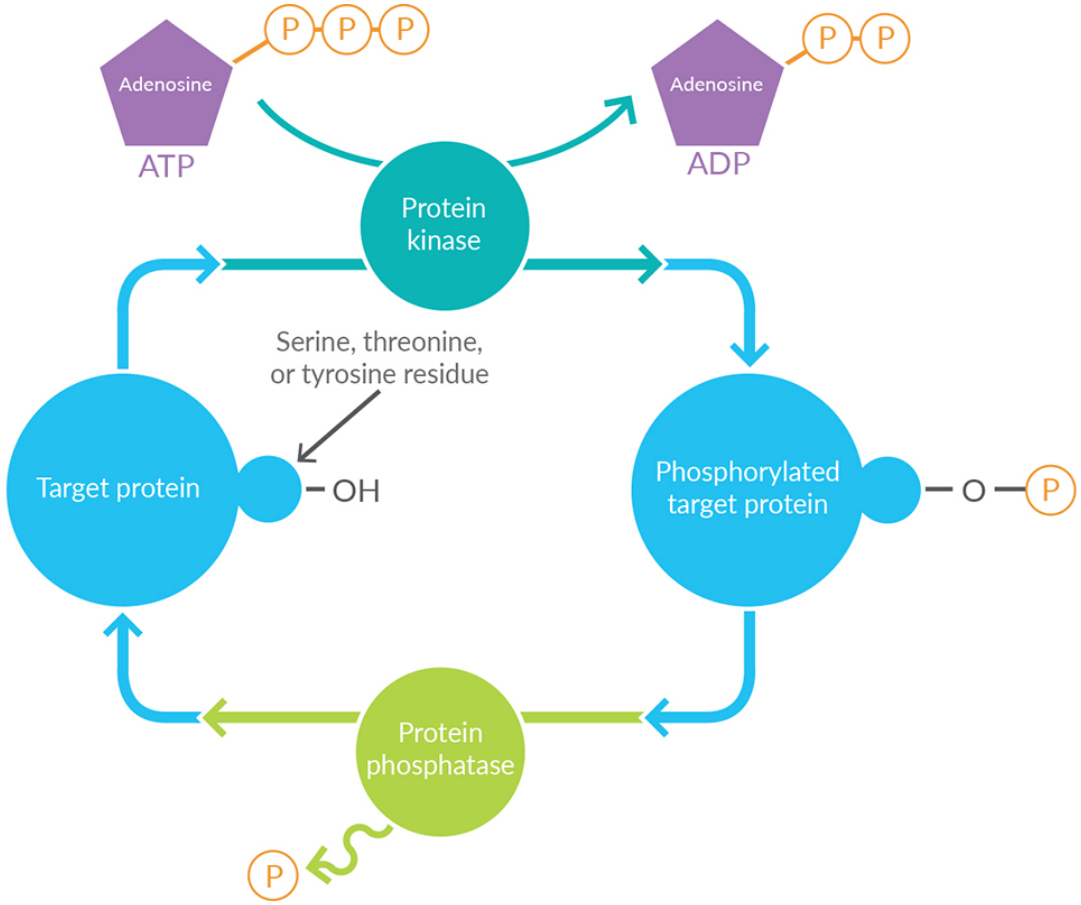
Wei Peng, Tuomas Varanka, Abdelrahman Mostafa, Henglin Shi, and Guoying Zhao, *Fellow, IEEE*

Abstract—Recently, hyperbolic deep neural networks (HDNNs) have been gaining momentum as the deep representations in the hyperbolic space provide high fidelity embeddings with few dimensions, especially for data possessing hierarchical structure. Such a hyperbolic neural architecture is quickly extended to different scientific fields, including natural language processing, single-cell RNA-sequence analysis, graph embedding, financial analysis, and computer vision. The promising results demonstrate its superior capability, significant compactness of the model, and a substantially better physical interpretability than its counterpart in the euclidean space. To stimulate future research, this paper presents a comprehensive review of the literature around the neural components in the construction of HDNN, as well as the generalization of the leading deep approaches to the hyperbolic space. It also presents current applications of various tasks, together with insightful observations and identifying open questions and promising future directions.

Index Terms—Neural networks on Riemannian manifold, hyperbolic neural networks, Poincaré model, Lorentz model

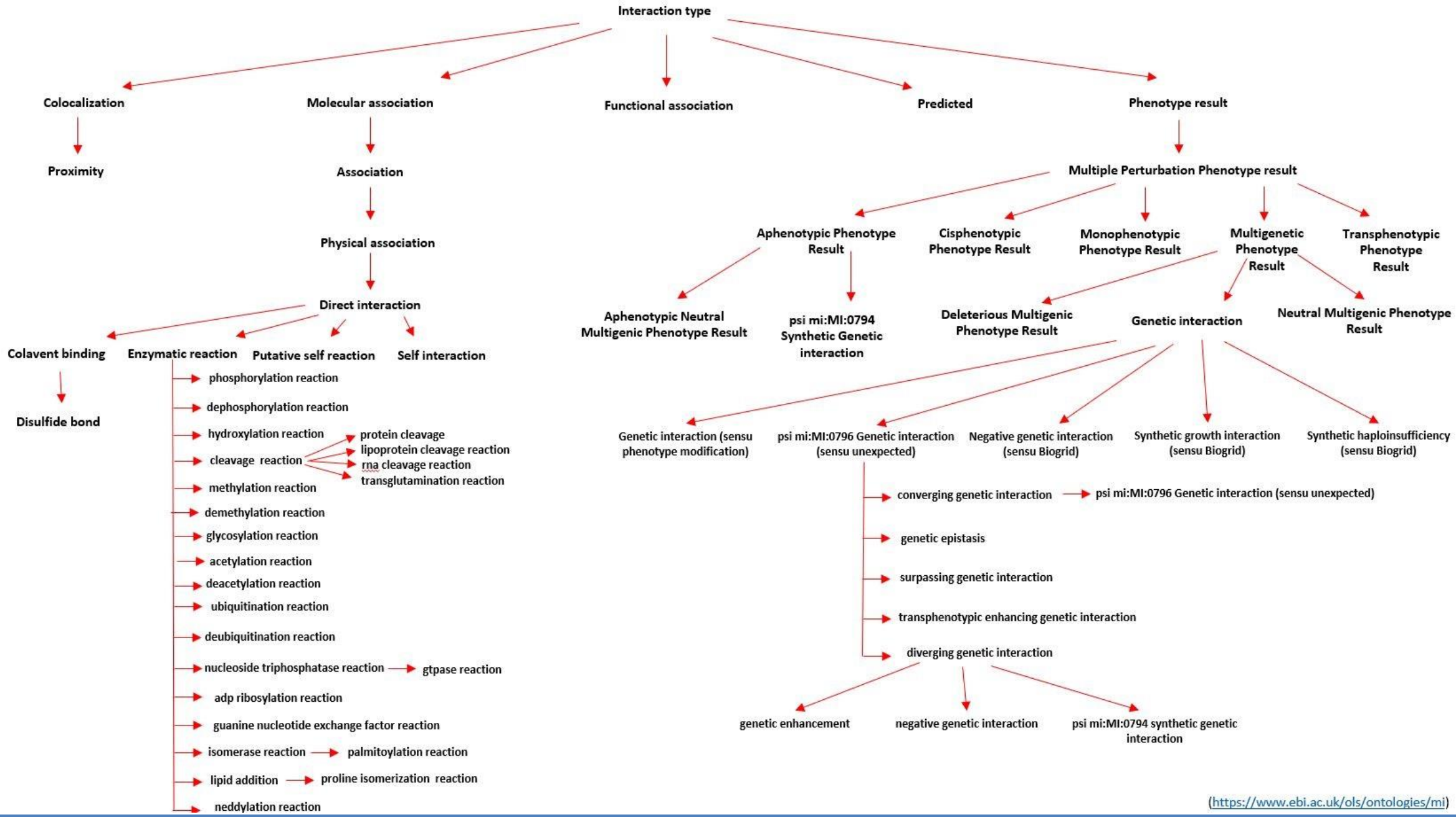
Function of PPIs





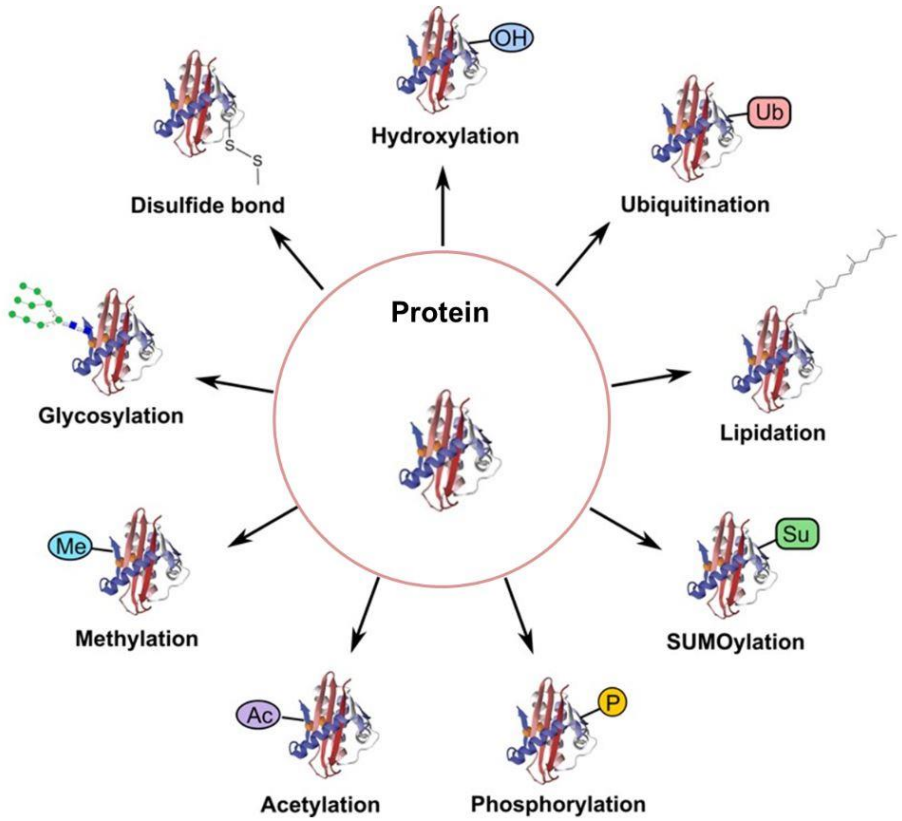
Molecular annotations of PPIs

The Molecular Interactions (MI) ontology forms a structured controlled vocabulary for the annotation of experiments concerned with protein-protein interactions.



(https://www.ebi.ac.uk/ols/ontologies/mi)

Why do we focus on PTMs?



frontiers in Cellular Neuroscience

REVIEW
published: 19 September 2018
doi: 10.3389/fncel.2018.00290

Roles of Post-translational Modifications in Spinocerebellar Ataxias

Linlin Wan[†], Keqin Xu[†], Zhao Chen[†], Beisha Tang[1,2,3,4,5,6,7] and Hong Jiang[1,2,3,4,8]*

[1] Department of Neurology, Xiangya Hospital, Central South University, Changsha, China, [2] National Clinical Research Center for Geriatric Diseases, Central South University, Changsha, China, [3] Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha, China, [4] Laboratory of Medical Genetics, Central South University, Changsha, China, [5] Parkinson's Disease Center of Beijing Institute for Brain Disorders, Beijing, China, [6] Collaborative Innovation Center for Brain Science, Shanghai, China, [7] Collaborative Innovation Center for Genetics and Development, Shanghai, China, [8] Department of Neurology, Xinjiang Medical University, Ürümqi, China

brain sciences

MDPI

Review

Do Post-Translational Modifications Influence Protein Aggregation in Neurodegenerative Diseases: A Systematic Review

Larissa-Nele Schaffert and Wayne G. Carter *

School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Uttoxeter Road, Derby DE22 3DT, UK; larissaschaffert@yahoo.de

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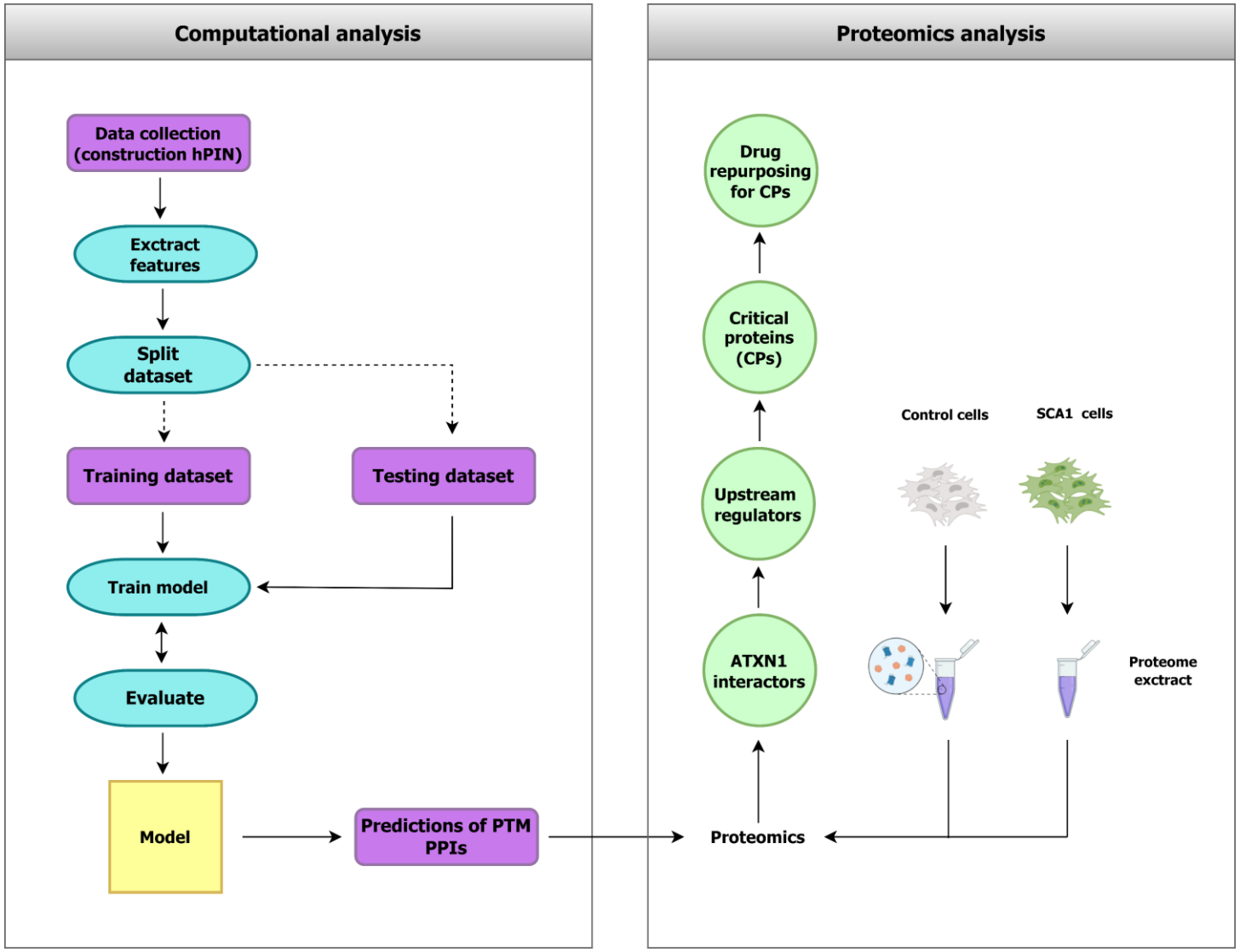
Review

Post-translational modifications: Regulators of neurodegenerative proteinopathies

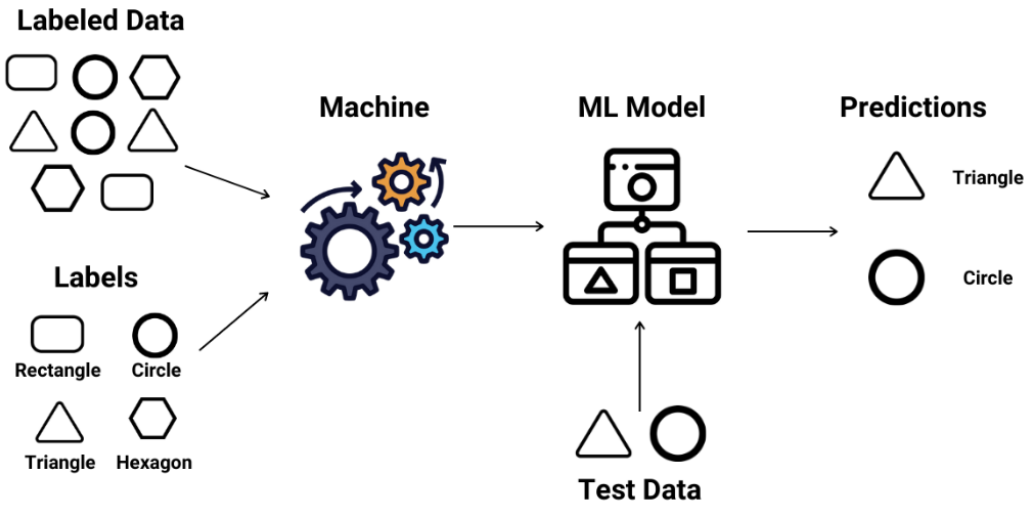
Rohan Gupta [1], Mehar Sahu [1], Devesh Srivastava [1], Swati Tiwari [1], Rashmi K. Ambasta, Pravir Kumar *

Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110042, India

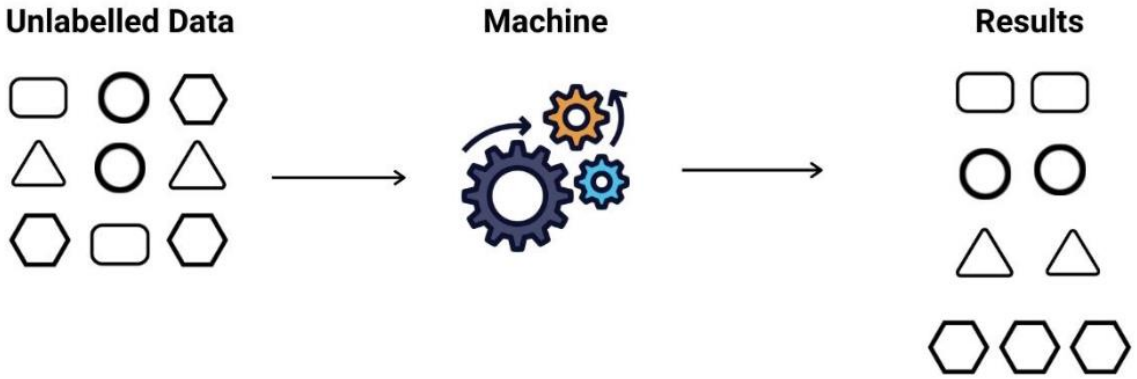

Computational analysis
Data collection (construction hPIN)
Exctract features
Split dataset
Training dataset
Testing dataset
Train model
Evaluate
Model
Predictions of PTM PPIs
Proteomics analysis
Drug repurposing for CPs
Critical proteins (CPs)
Upstream regulators
ATXN1 interactors
Proteomics
Control cells
SCA1 cells
Proteome exctract

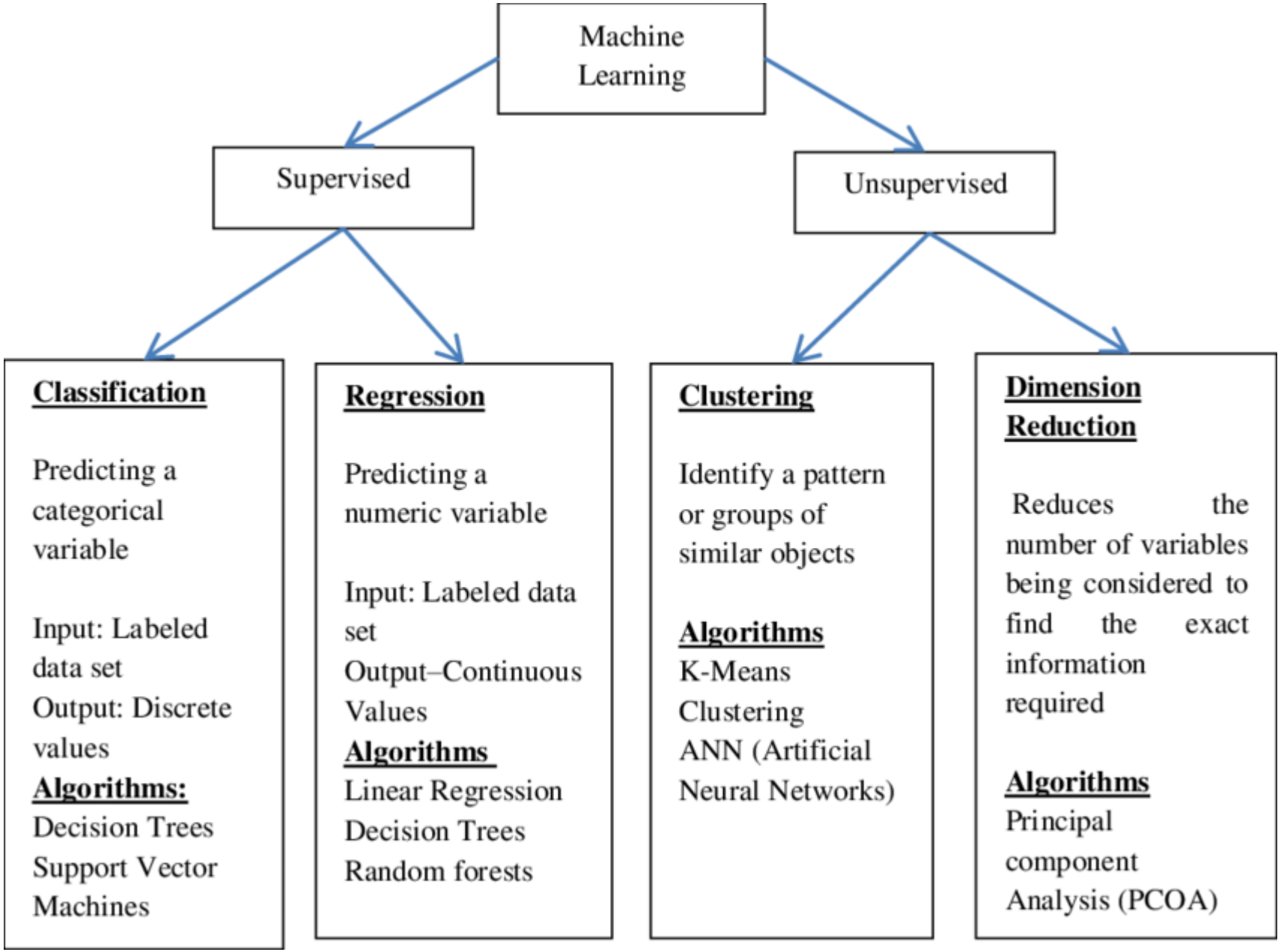
What is machine learning?

Supervised Learning

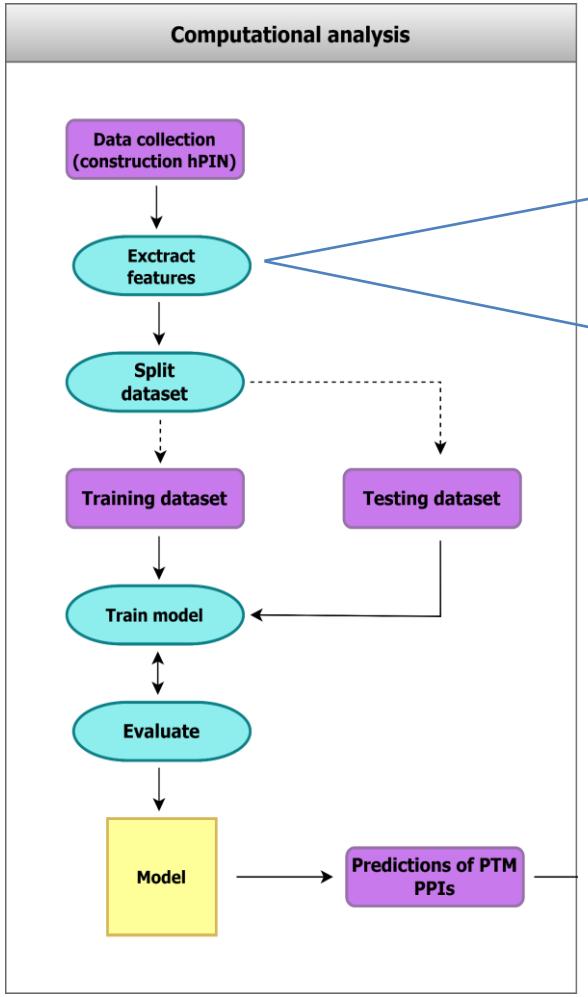


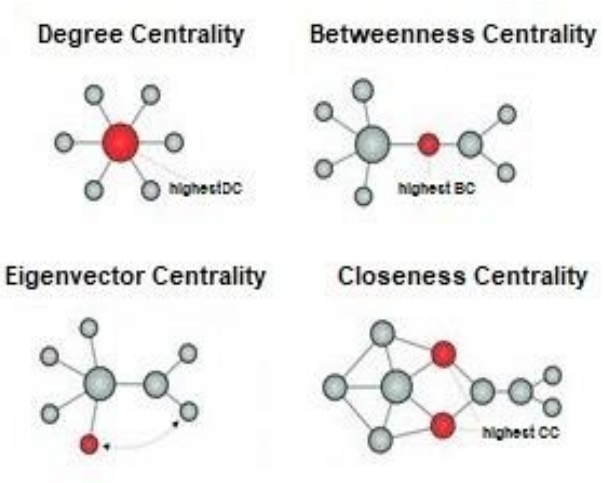
Unsupervised Learning



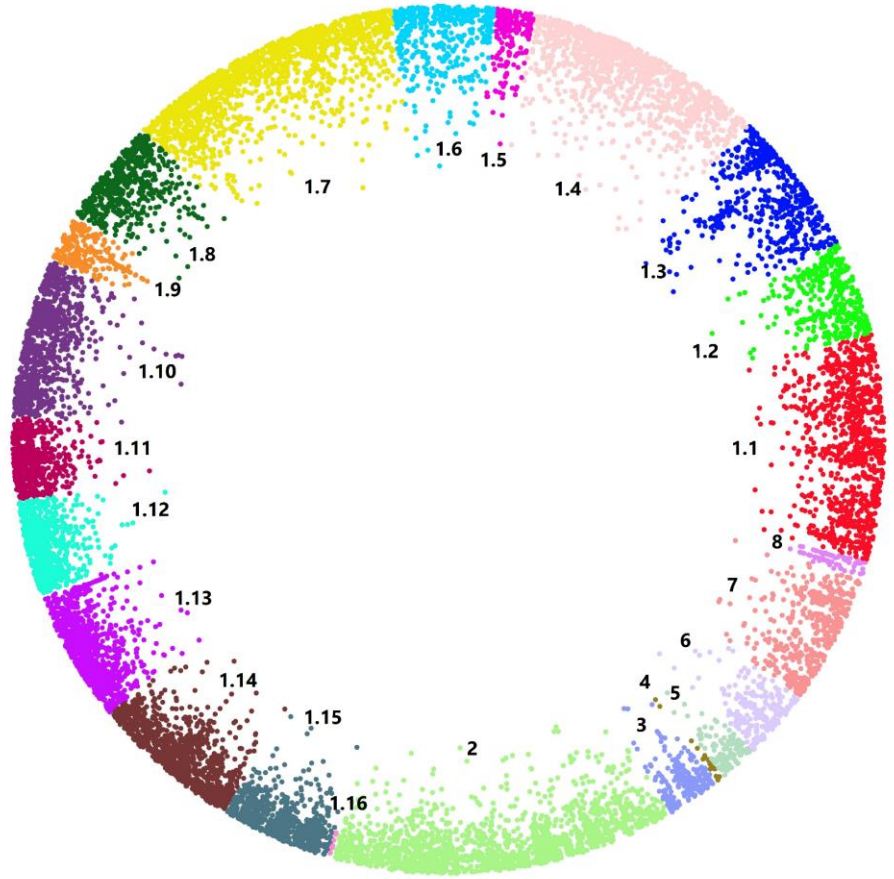

Machine Learning
Supervised
Unsupervised
Classification
Predicting a categorical variable
Input: Labeled data set
Output: Discrete values
Algorithms:
Decision Trees
Support Vector Machines
Regression
Predicting a numeric variable
Input: Labeled data set
Output–Continuous Values
Algorithms
Linear Regression
Decision Trees
Random forests
Clustering
Identify a pattern or groups of similar objects
Algorithms
K-Means Clustering
ANN (Artificial Neural Networks)
Dimension Reduction
Reduces the number of variables being considered to find the exact information required
Algorithms
Principal component Analysis (PCOA)

Features





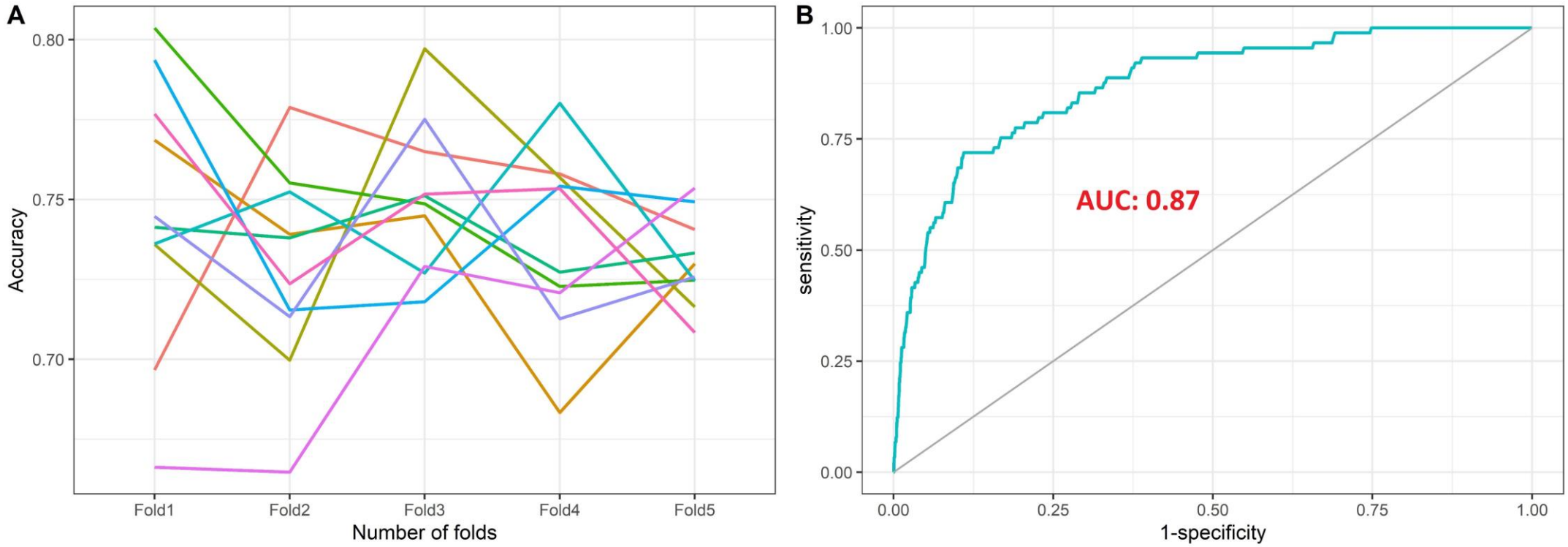
A



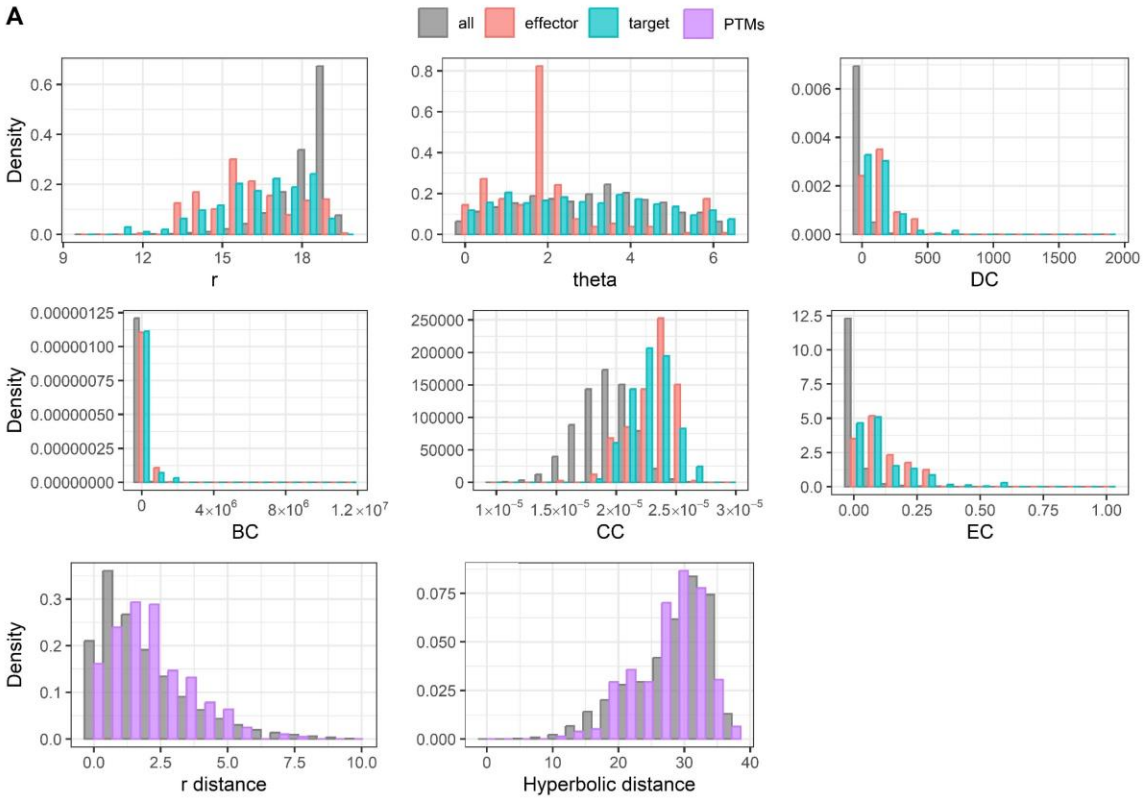
B

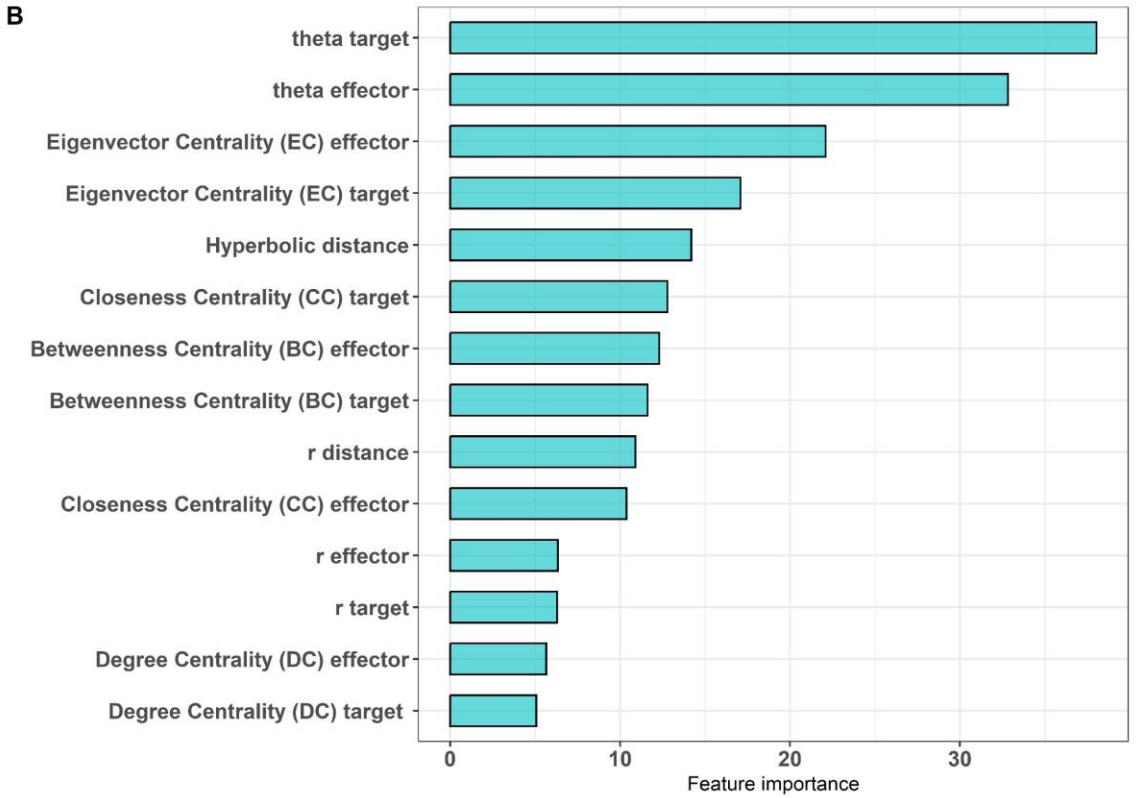
Cluster	GO BP Terms	Cluster	GO BP Terms
1.1	mRNA processing	1.13	mitochondrial translational elongation
1.2	regulation of gene silencing by miRNA	1.14	mitochondrial respiratory chain complex assembly
1.3	regulation of nucleobase-containing compound metabolic process	1.15	sphingolipid metabolic process
1.4	alpha-amino acid biosynthetic process	1.16	regulation of angiotensin levels in blood
1.5	cell cycle G1/S phase transition	2	regulation of cell cycle G2/M phase transition
1.6	post-translational protein modification	3	intraciliary retrograde transport
1.7	protein ubiquitination	4	N-terminal protein amino acid modification
1.8	positive regulation of establishment of protein localization to telomere	5	positive regulation of tyrosine phosphorylation of STAT protein
1.9	regulation of cellular amine metabolic process	6	positive regulation of lipopolysaccharide-mediated signaling pathway
1.10	metanephric renal vesicle morphogenesis	7	chemokine-mediated signaling pathway
1.11	protein transport	8	regulation of DNA-templated transcription, initiation
1.12	protein insertion into ER membrane by stop-transfer membrane-anchor sequence		

RF model

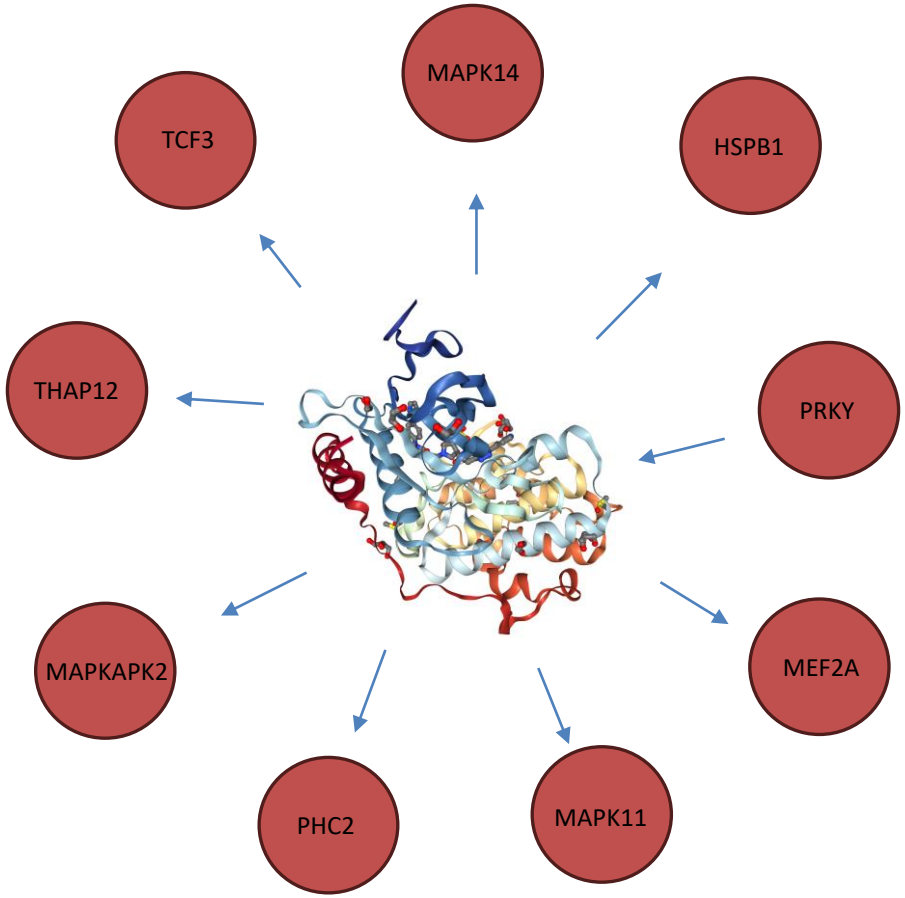

A
0.80
0.75
0.70
Accuracy
Fold1
Fold2
Fold3
Fold4
Fold5
Number of folds
B
1.00
0.75
0.50
0.25
0.00
sensitivity
AUC: 0.87
0.00
0.25
0.50
0.75
1.00
1-specificity

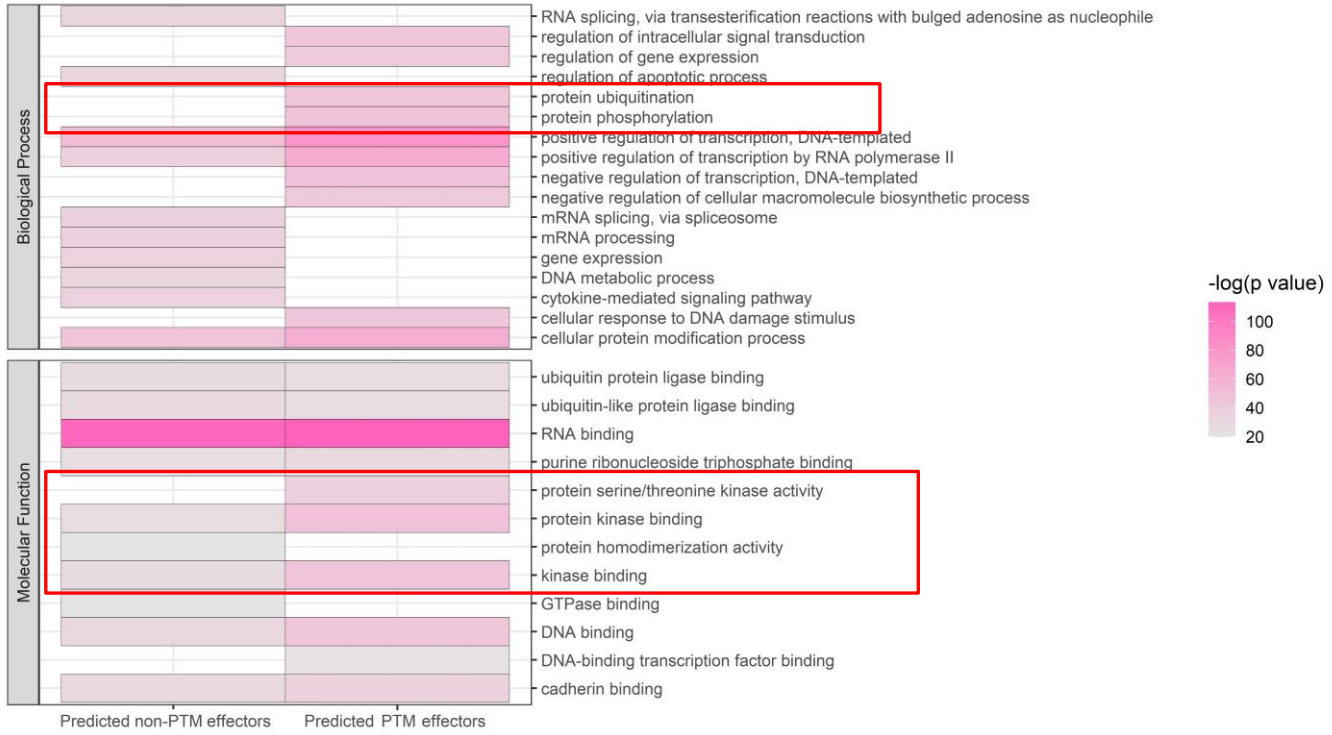
Feature importance



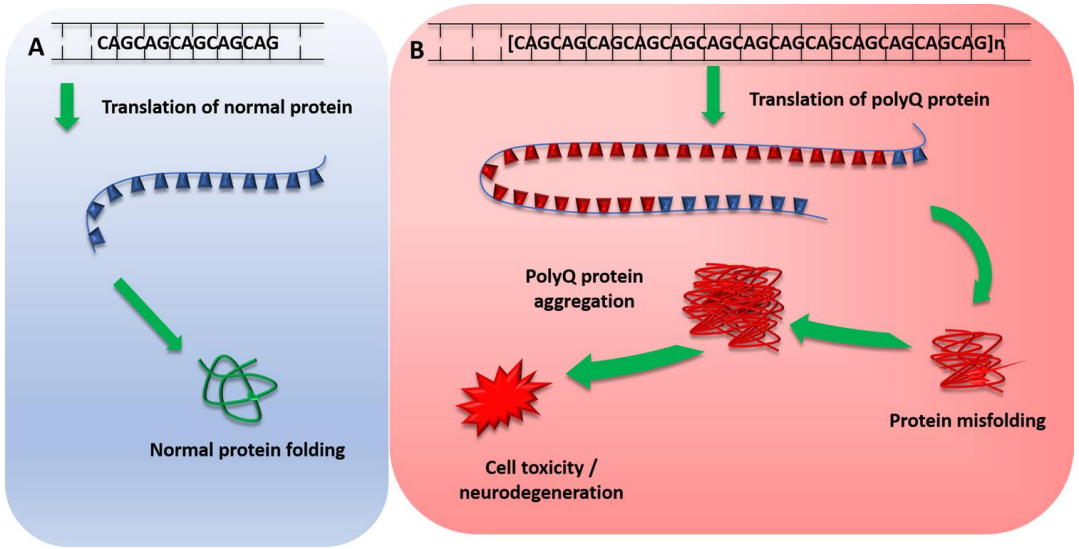


MAPK3 protein kinase

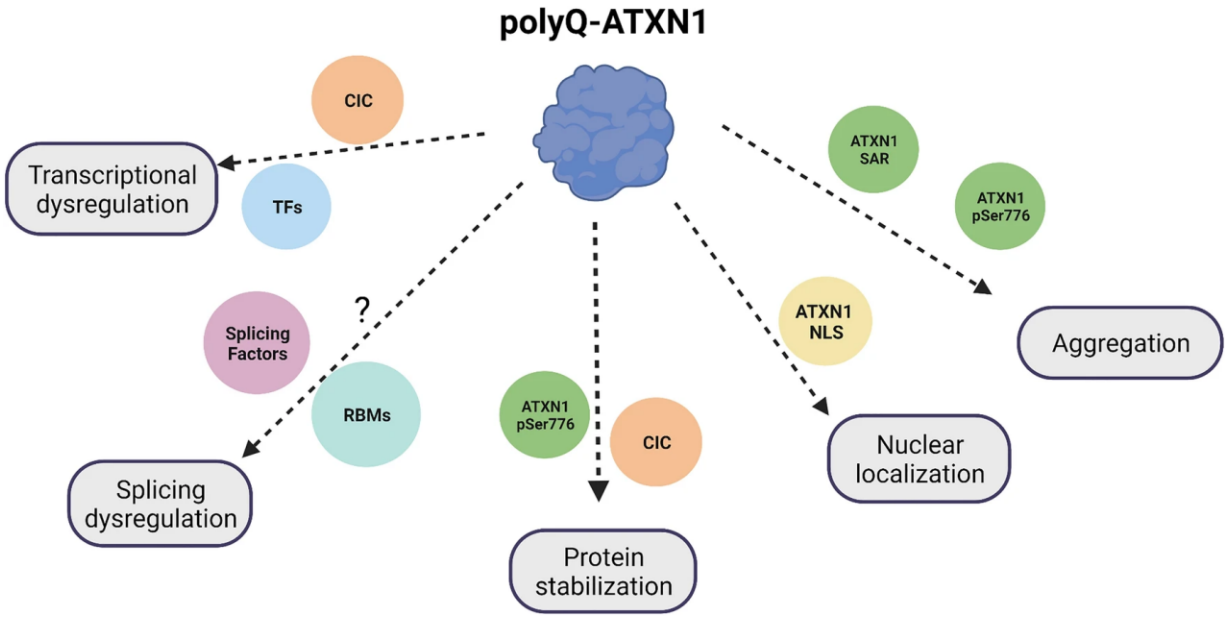




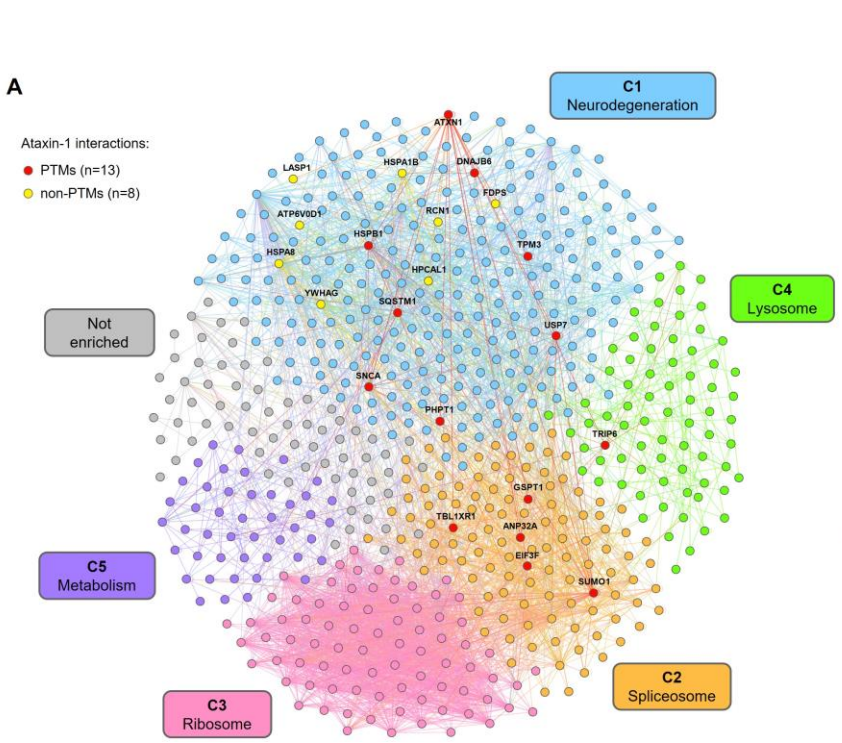
Spinocerebellar ataxia 1 (SCA1)

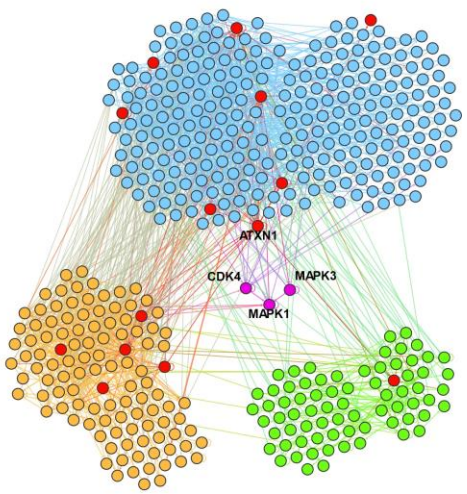


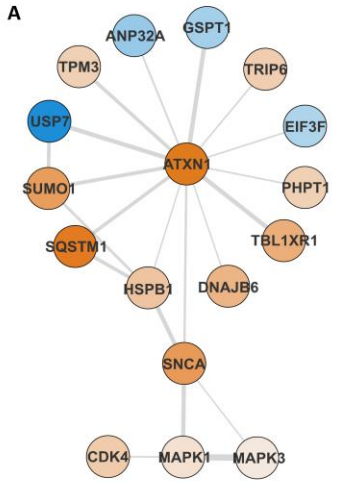
Molecular mechanisms of SCA1 pathogenesis

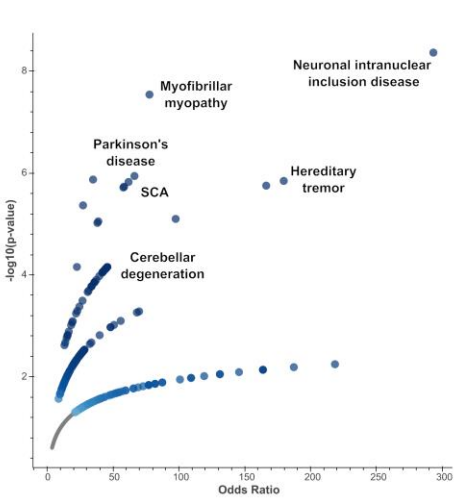


SCA1 cell model- Predicted PTMs







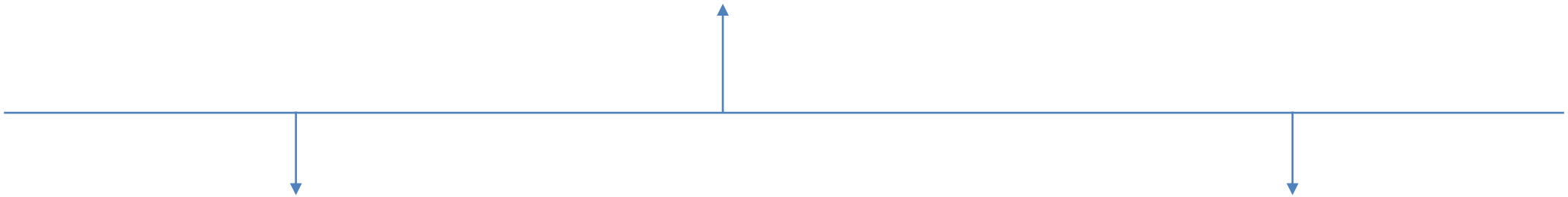


C

Drug candidate	Reverse score	Administration
artesunate	25%	Malaria
BRD-K54687541	25%	Unknown
betamethasone	25%	cerebral edema, congenital adrenal hyperplasia
budesonide	25%	Crohn's disease, asthma, allergies
BRD-K71265179	25%	Unknown
Linifanib	25%	hematologic malignancies, solid tumors
BRD-A08662020	25%	Unknown

Next steps

Experimental validation
of the predicted directed PTMs



Experimental verification of the
suggested drugs

Explore hyperbolic geometry
in different biological data

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- Zahra NuA, Vagiona AC, Uddin R, Andrade-Navarro MA. Selection of Multi-Drug Targets against Drug-Resistant Mycobacterium tuberculosis XDR1219 Using the Hyperbolic Mapping of the Protein Interaction Network. Int. J. Mol. Sci. 2023, 24, 14050
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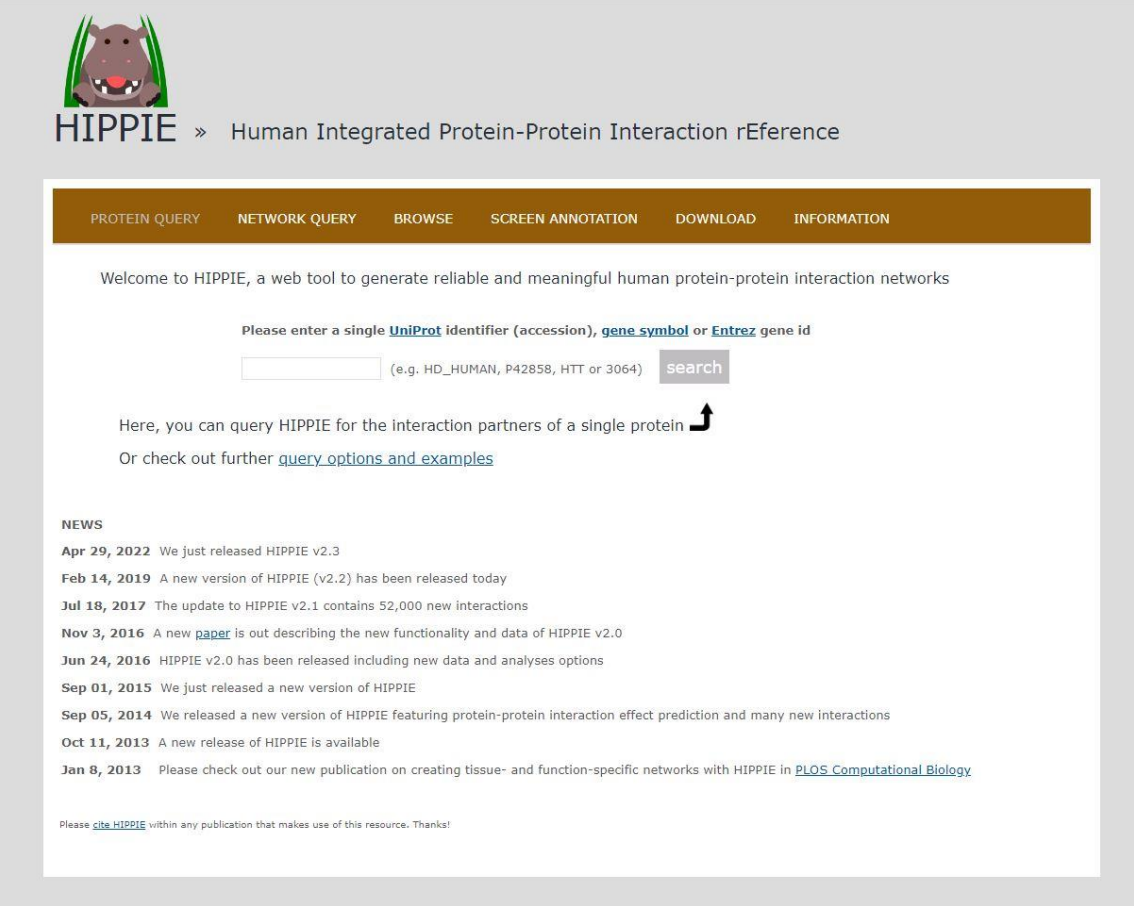
Acknowledgments

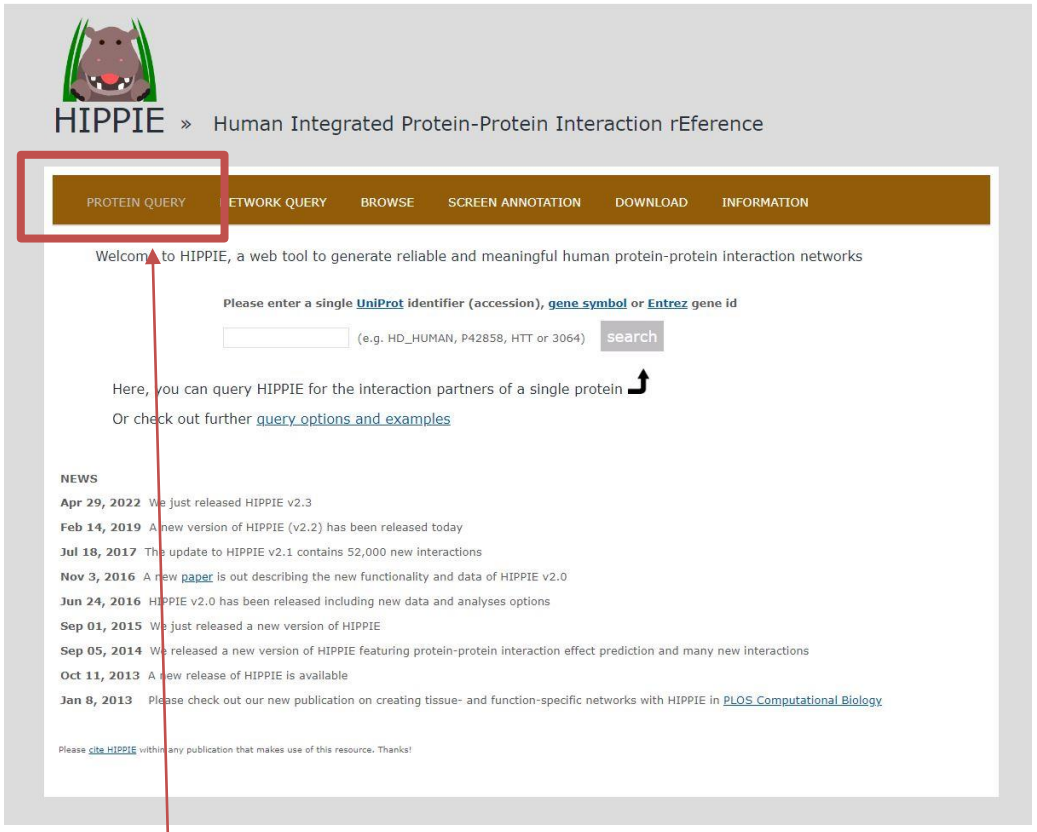
Lovely to meet you all !!!!!

Thank you!
Any questions?

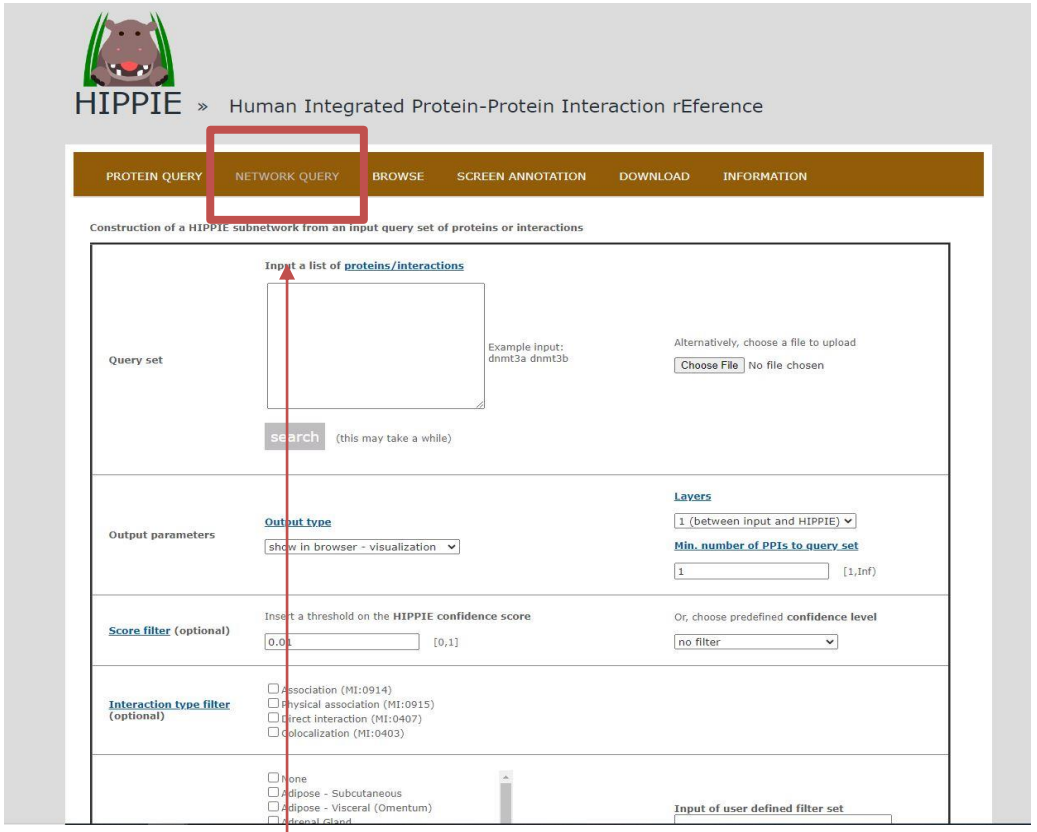
Let’s play…



http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/

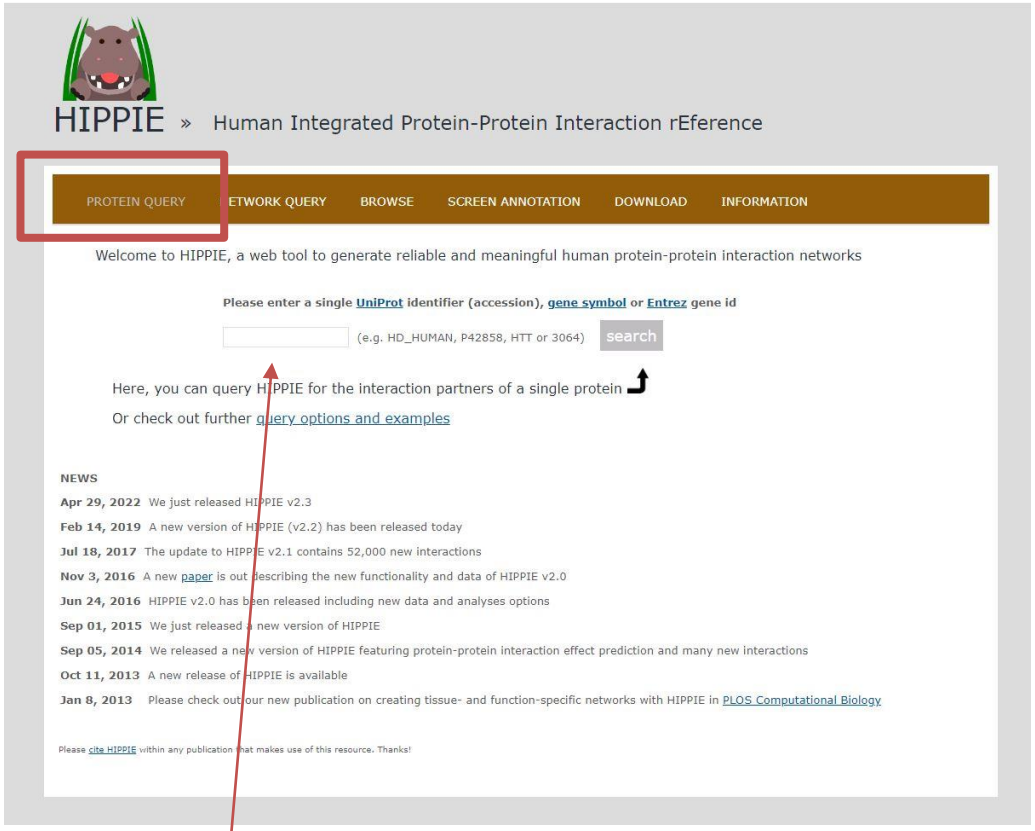


Input: one protein

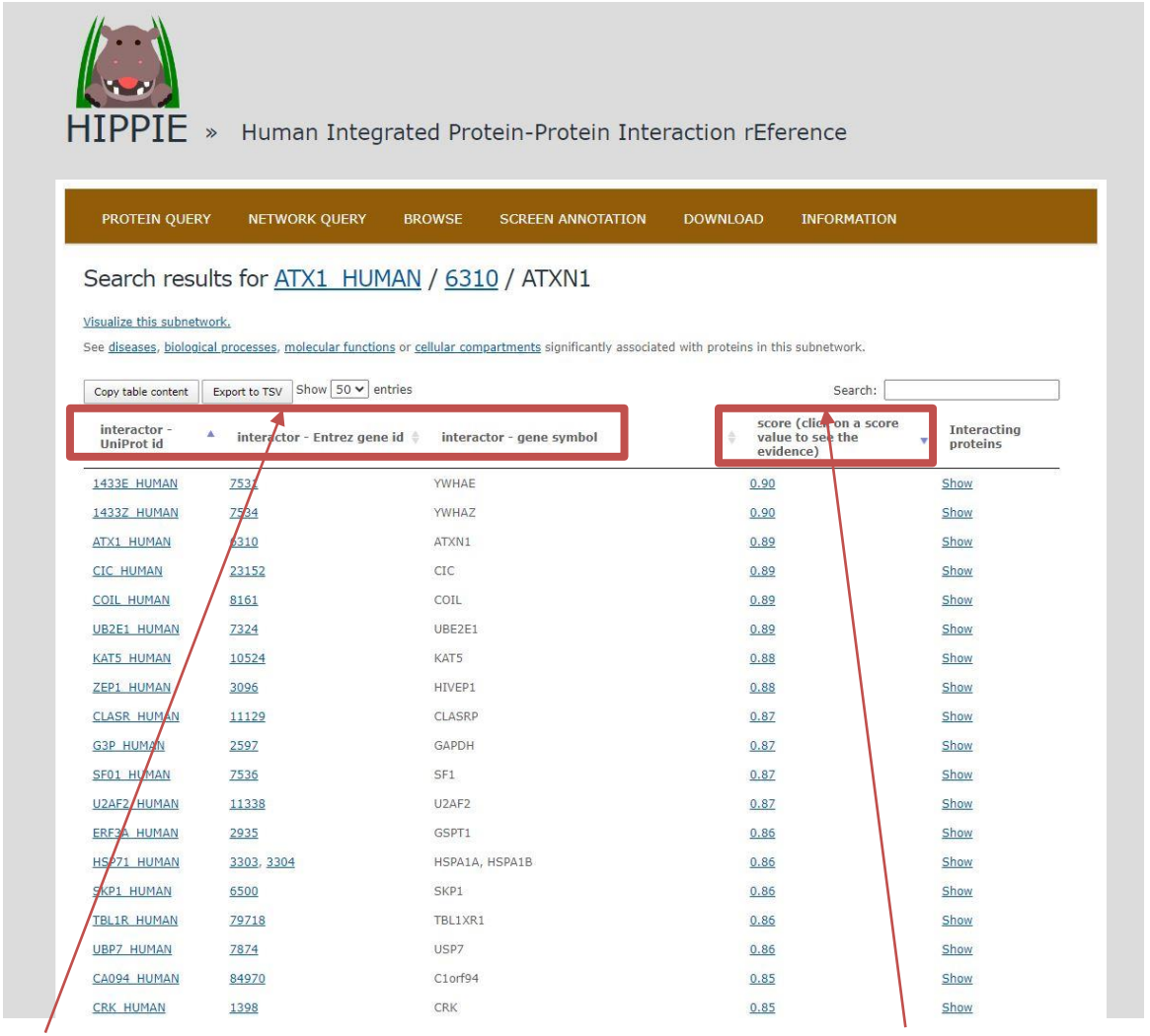


Input: list of protein

How many interactors ATXN1 has?



Search: ATXN1



Interactors of ATXN1

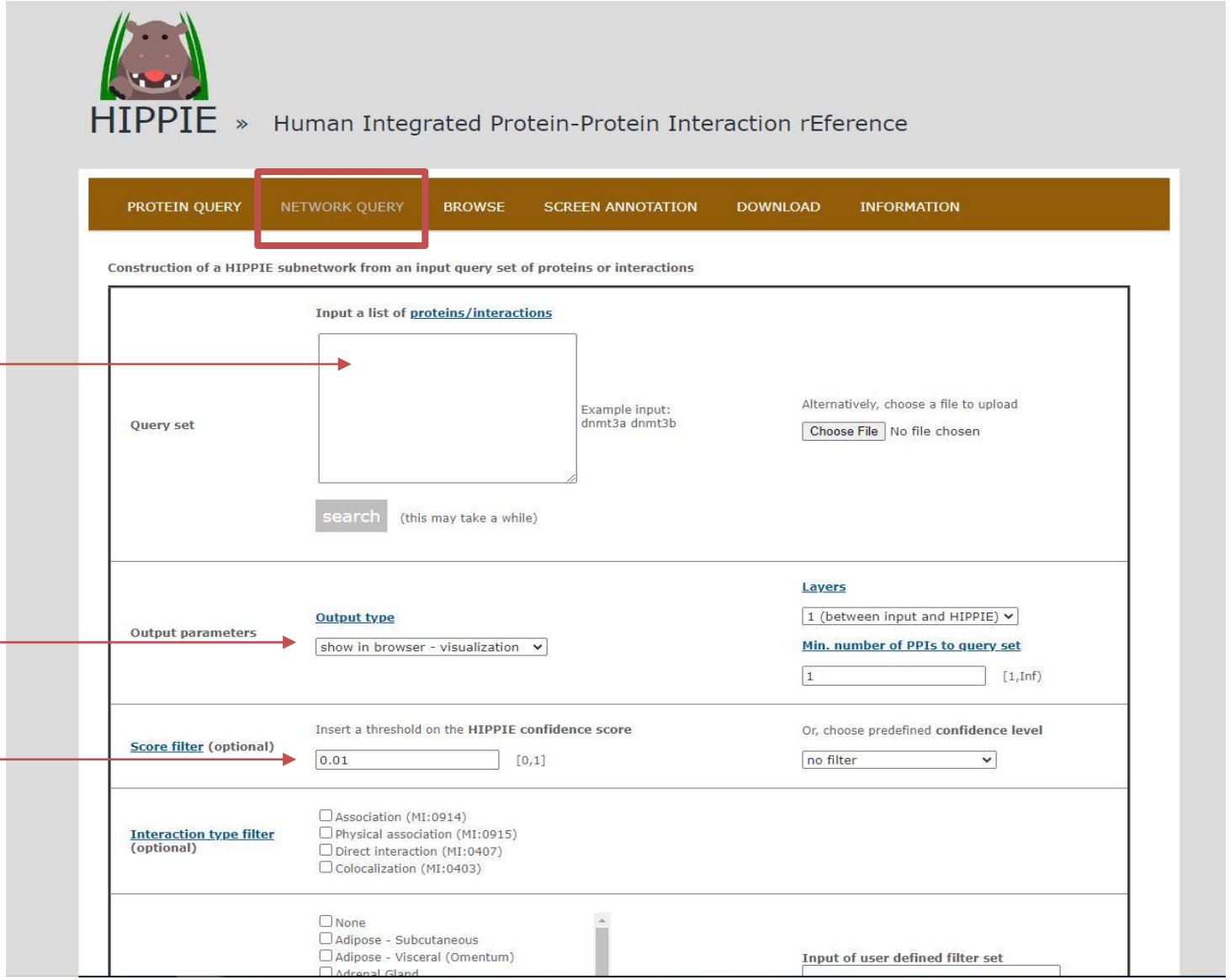
confidence score

How many interactors ATXN1 has with confidence score more than 0.71?

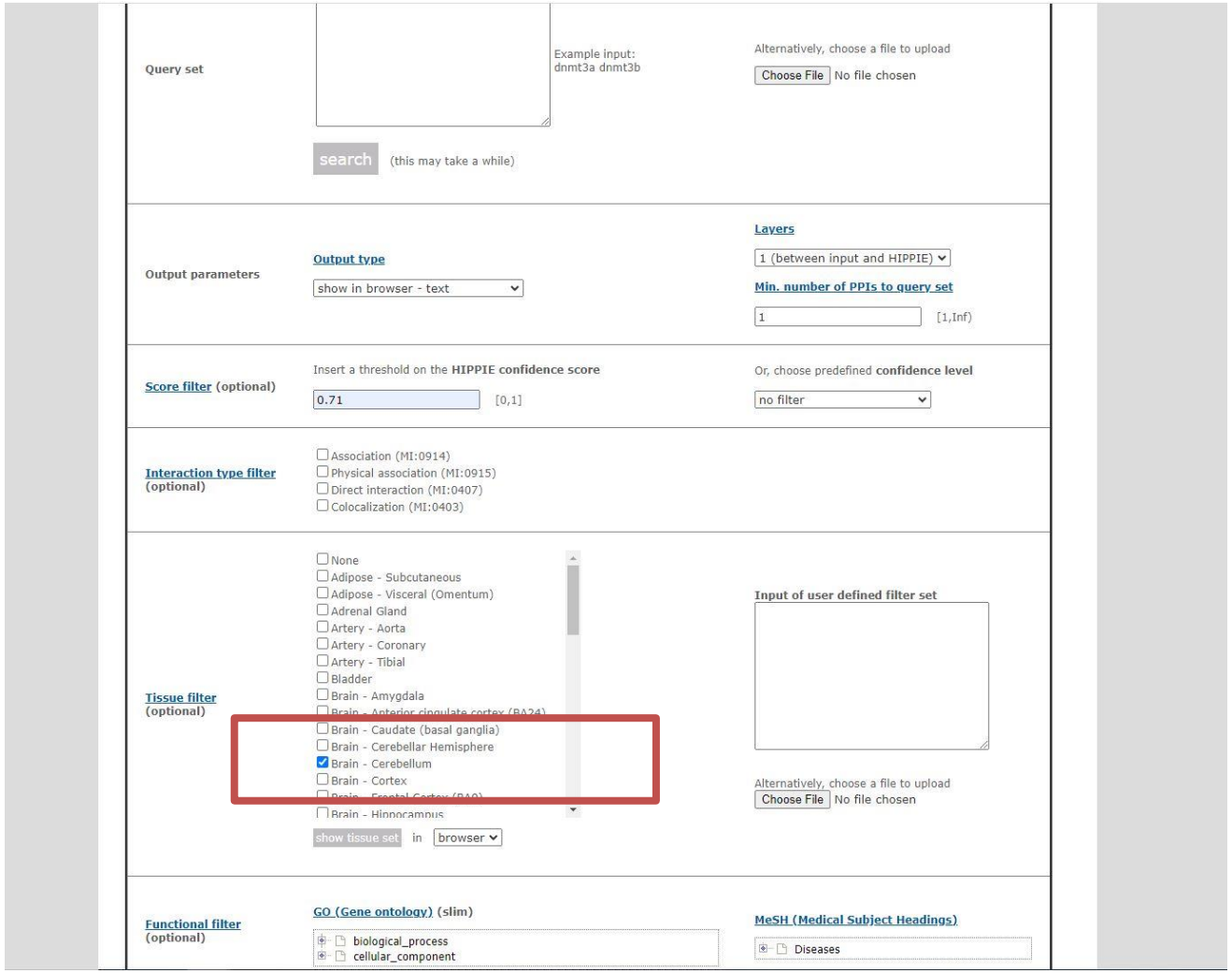
Search: ATXN1

text

set to 0.71



How many interactors ATXN1 has with confidence score more than 0.71 that are expressed in the cerebellum?



How many interactors ATXN1 has, with confidence score more than 0.71 that are expressed in the cerebellum and associated with neurodegenerative disease?