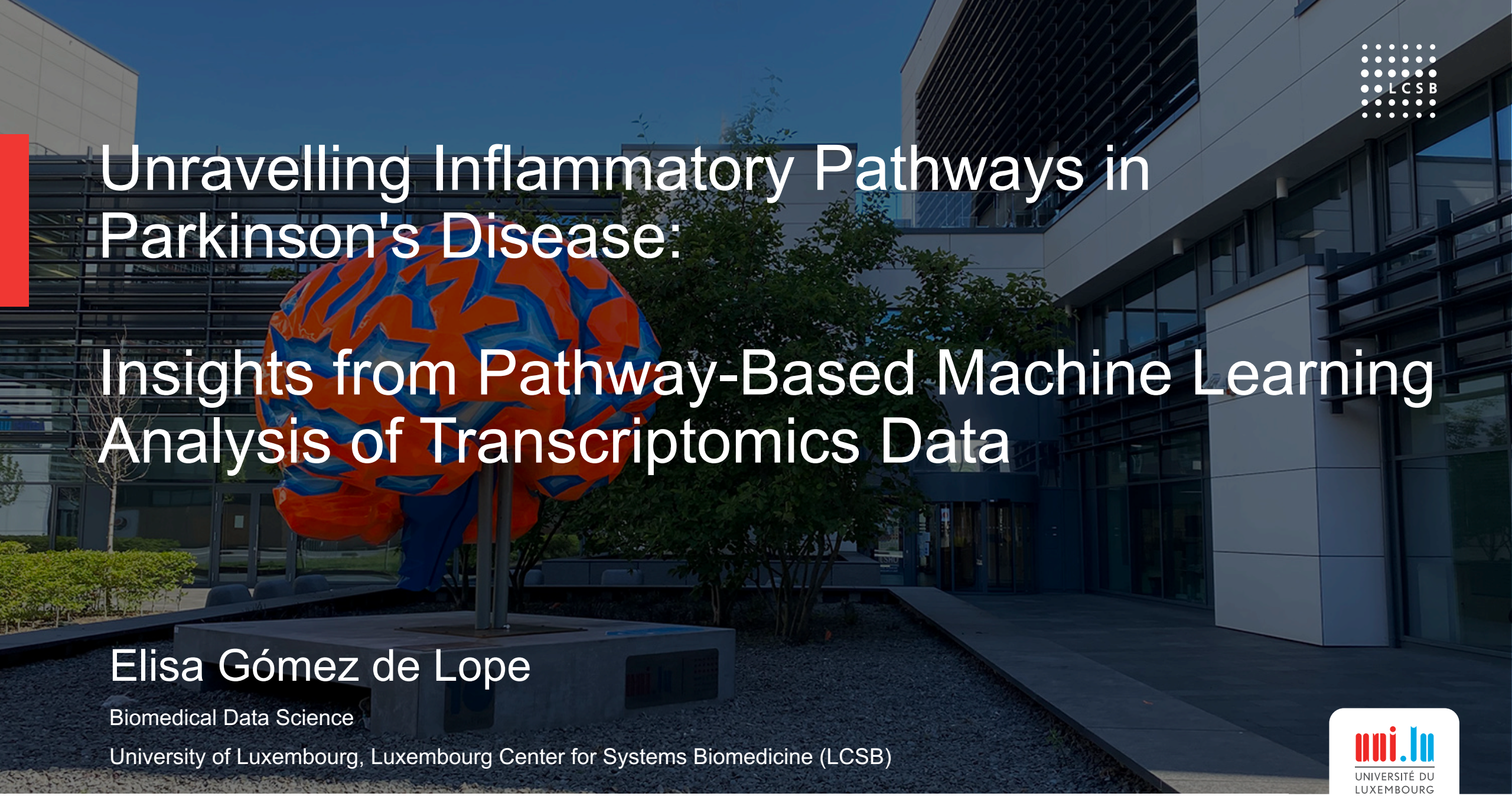


Unravelling Inflammatory Pathways in Parkinson's Disease:

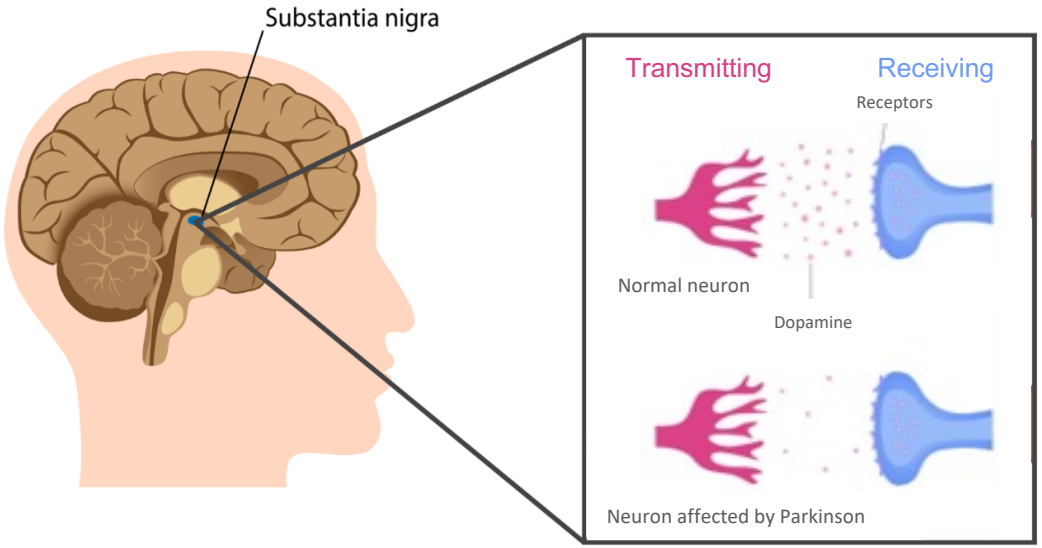
Insights from Pathway-Based Machine Learning Analysis of Transcriptomics Data

Elisa Gómez de Lope

Biomedical Data Science

University of Luxembourg, Luxembourg Center for Systems Biomedicine (LCSB)

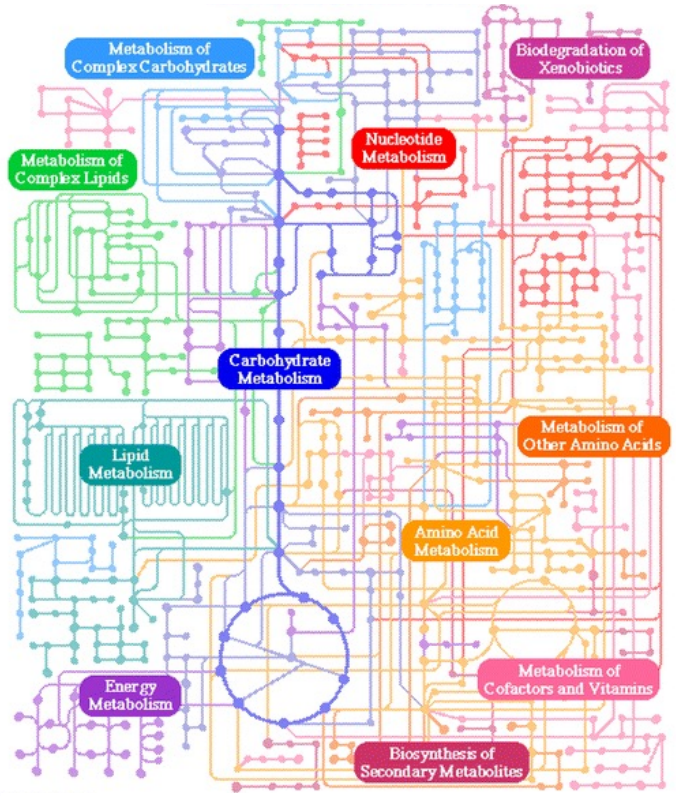
Parkinson's Disease & higher order functional representations



Source: Adapted from shutterstock

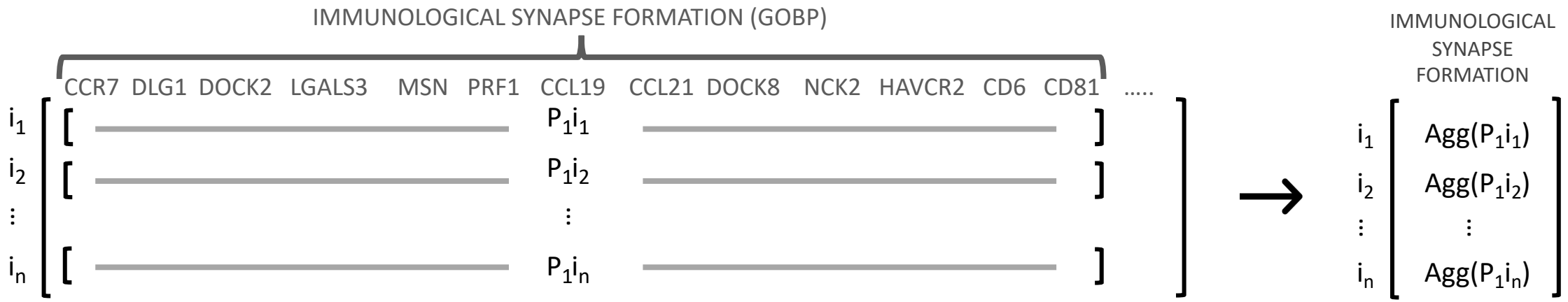
- Single gene mutations?
- Mitochondrial genetics?
- Environmental factors (toxins)?

Diagnosis is clinical & difficult

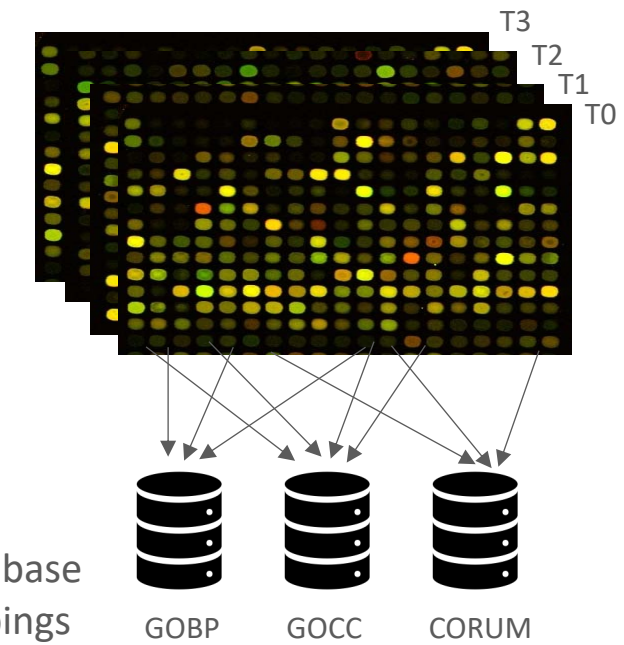


Schematic representation of metabolic networks
Source: The Origin and Evolution of Metabolic Pathways: Why and How did Primordial Cells Construct Metabolic Routes?

Generation of higher order functional features (I)

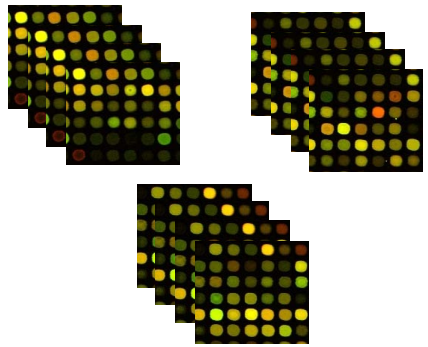


Temporal gene expression matrices (4xmxn)



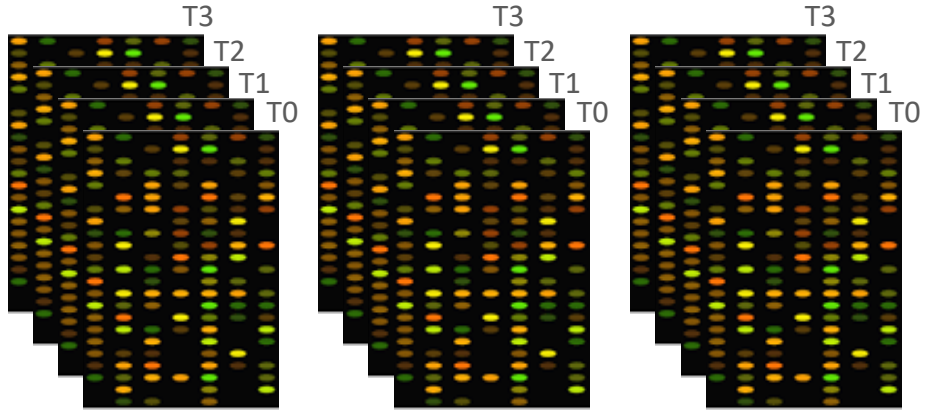
3 Database Mappings

Aggregation based on GOBP, GOCC & CORUM mappings



Aggregation statistics + PCA, Pathifier's dimension reduction-derived deregulation scores

3x Temporal aggregated expression matrices (4xmxp)



Longitudinal analyses

Transcriptomics aggregated temporal profiles

Feature selection strategies on transcriptomics data for a Random forest predictive model of PD diagnosis

			GOBP		GOCC		CORUM	
Ft. selection	**N ft. cutoff**	**GENES**	**mean**	**sd**	**mean**	**sd**	**mean**	**sd**
DEA	10	0.58 ± 0.05	0.55 ± 0.06	0.54 ± 0.03	0.54 ± 0.05	0.57 ± 0.05	0.55 ± 0.04	0.55 ± 0.06
DEA	100	0.59 ± 0.06	0.58 ± 0.06	0.57 ± 0.06	0.54 ± 0.07	0.56 ± 0.07	0.55 ± 0.05	0.55 ± 0.06
DEA	1000	0.56 ± 0.07	0.54 ± 0.09	0.56 ± 0.06	0.55 ± 0.06	0.55 ± 0.07	-	-
Lasso	-	**0.63 ± 0.08**	**0.64 ± 0.09**	**0.60 ± 0.11**	**0.59 ± 0.05**	**0.63 ± 0.1**	0.54 ± 0.1	**0.66 ± 0.07**
Pearson corr.	-	0.59 ± 0.06	0.57 ± 0.06	0.56 ± 0.06	0.56 ± 0.05	0.56 ± 0.06	**0.56 ± 0.04**	0.56 ± 0.05
No selection	-	0.58 ± 0.06	0.57 ± 0.05	0.57 ± 0.05	0.56 ± 0.05	0.57 ± 0.05	0.55 ± 0.05	0.56 ± 0.04

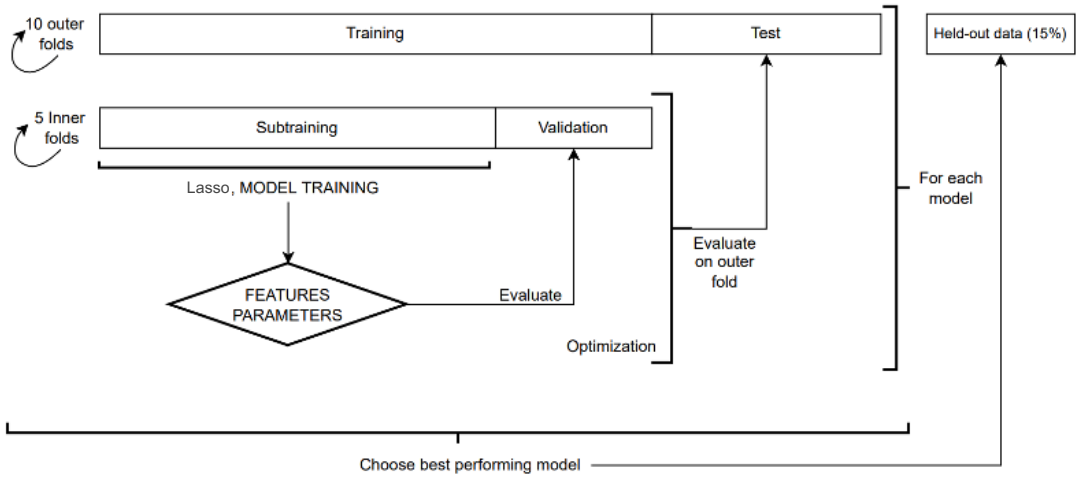
Table 4.1 Predictive performance for PD diagnosis measured as average cross-validated AUC ± standard deviation from gene expression data at gene and aggregated levels (mean and standard deviation) using DEA filter, Lasso penalty, a Pearson correlation filter (0.85) and no feature selection at all on a random forest model.

Lasso penalty obtained highest cross-validated AUC in a Random Forest model across most transcriptomics-based datasets.

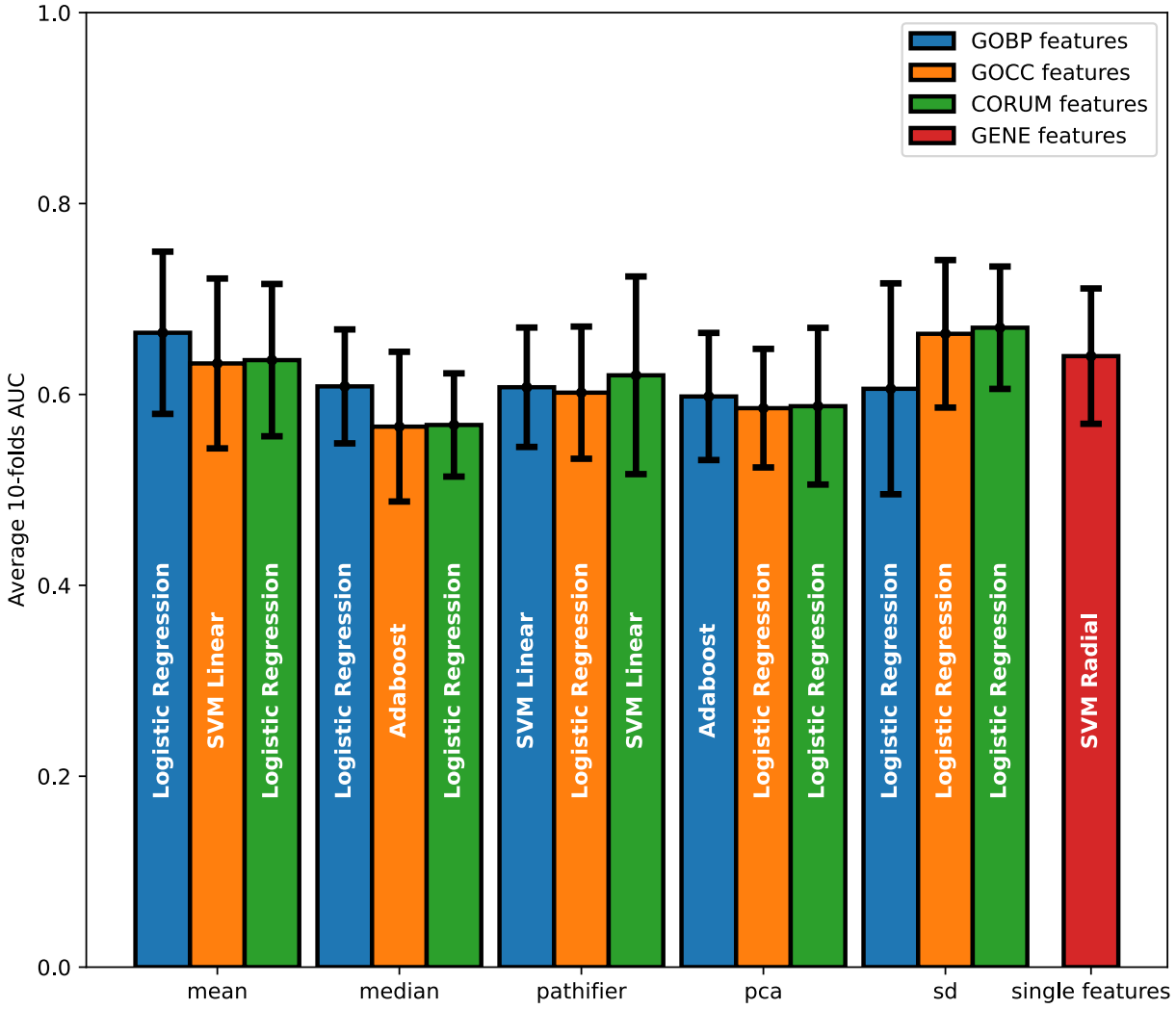
Predictive PD diagnosis with ML models on transcriptomics data

Models:
Logistic regression
Random Forest
SVM (Linear kernel)
SVM (Radial kernel)
Adaboost
Gradient boosting

Feature selection: Lasso penalty regression

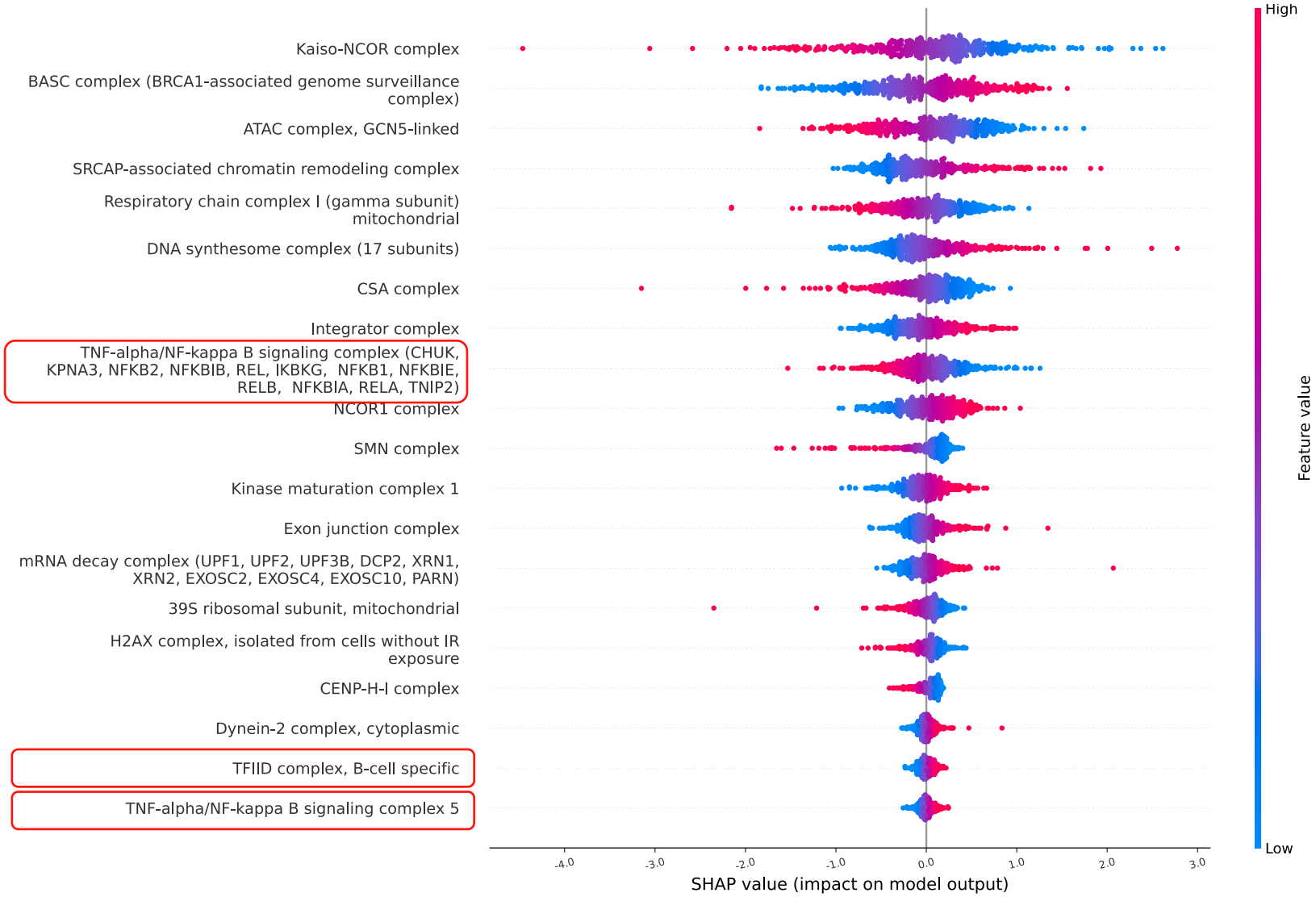


Crossvalidated AUC scores from best performing model on transcriptomics-based datasets



Relevant features from predictive PD diagnosis

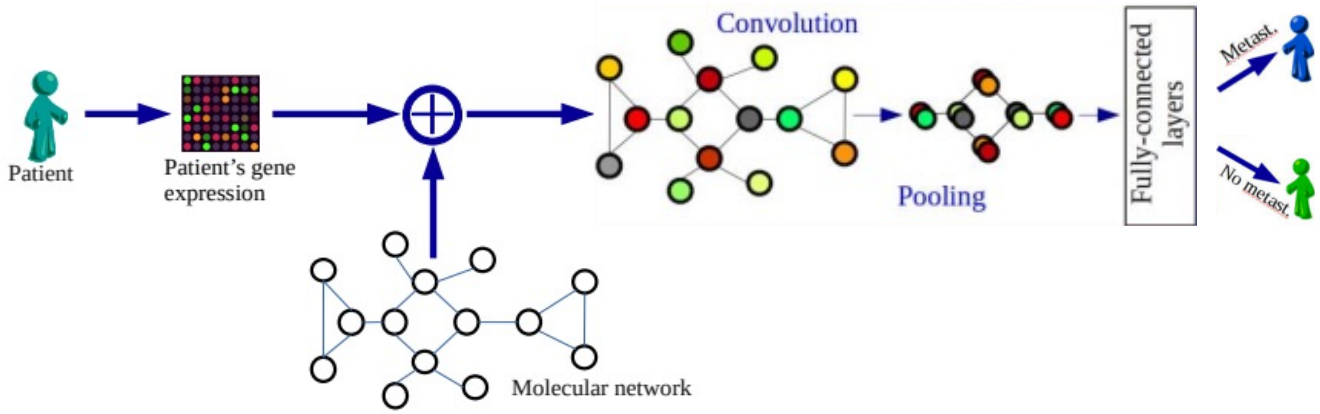
Shap values of (SD -aggregated) protein complexes (CORUM) predictors on Logistic Regression model



Limitations & outlook for future analyses

- ✗ Unknown confounders
- ✗ Large variability among PD patients makes identifying common trends difficult
- ✗ Data represents late stages of the disease

- ➡ Modelling other PD prognostic outcomes (e.g. motor dysfunction scores)
- ➡ Use a graph representation of the data via protein-protein interactions network



Gene expression profile as a graph signal of the molecular network

Source: Chereda, H., 2022. Explaining decisions of graph convolutional neural networks for analyses of molecular subnetworks in cancer [Doctoral thesis, Georg-August-Universität Göttingen]

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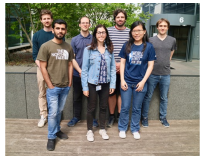

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