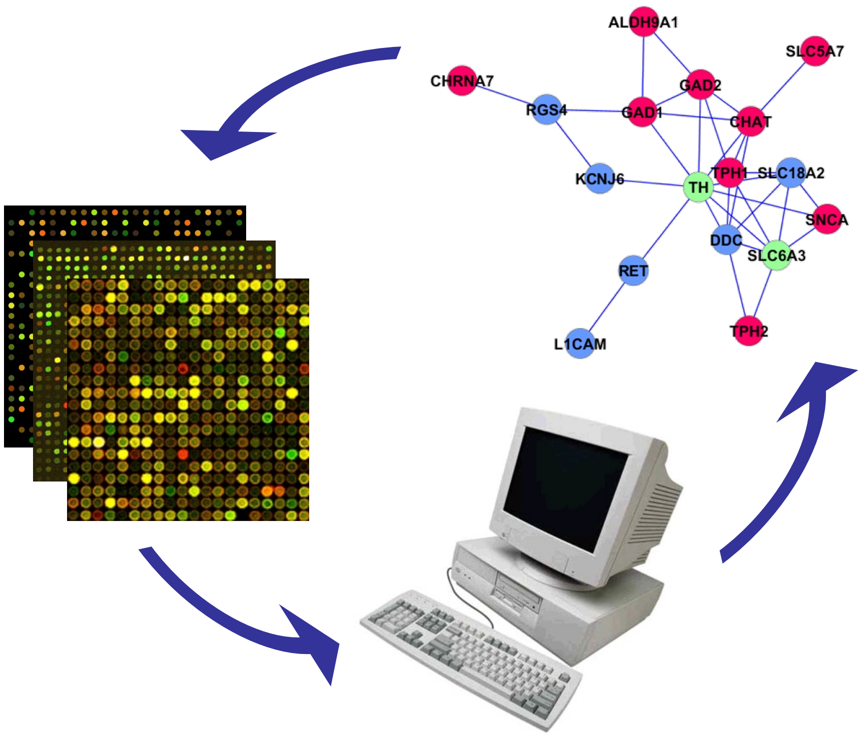

Omics network analysis using mathematical programming

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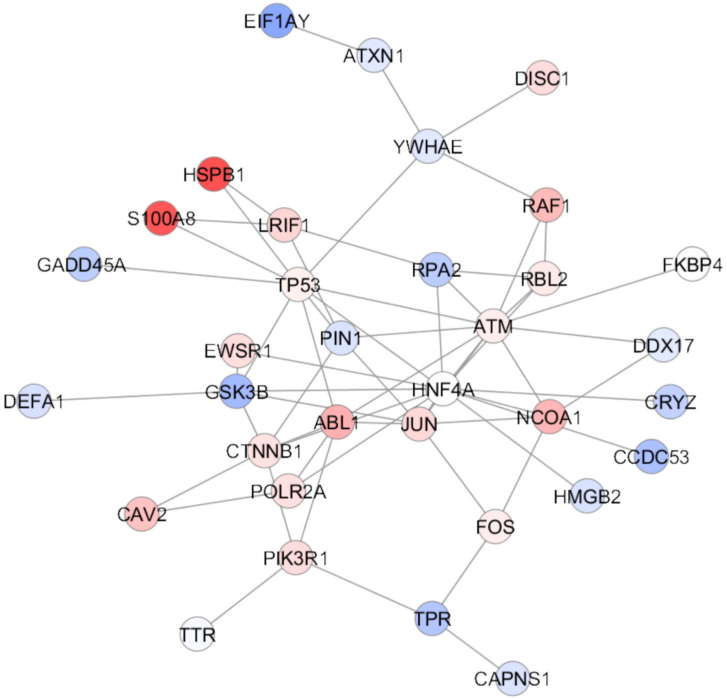
Motivation

Disease-associated molecular perturbations are often localized in biological networks. Finding these network clusters may help us to develop more robust biomarker models.



Example sub-network for Parkinson‘s disease (PD):

🔴 Over-expressed in PD

🔵 Under-expressed in PD

Question: How can we find clustered gene/protein groups efficiently, accounting for their predictivity and connectedness in the network?

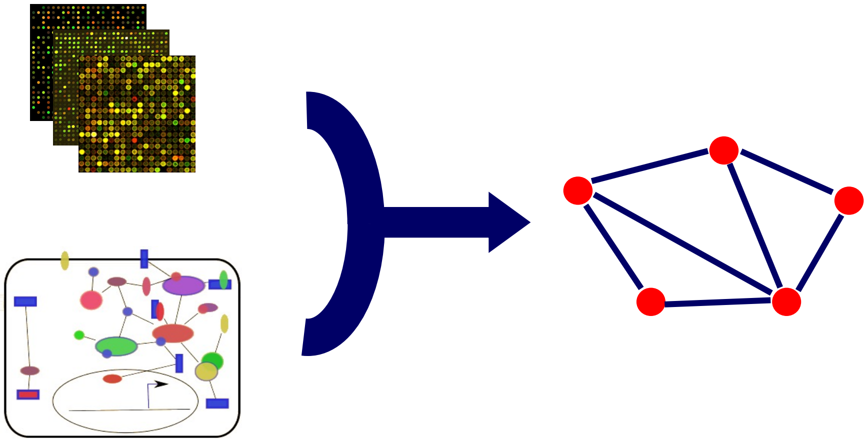
GenePEN - Workflow

Input:

- Gene/protein expression dataset **X** (p rows = genes, n columns = samples)
- Class labels **y** (e.g., “patient vs. control”, “disease subtype 1 vs. disease subtype 2”)
- Table **A** of interactions/similarities between rows in X (e.g., protein-protein interactions)

Output:

- A subset of discriminative genes (rows in X) representing a **connected** component in A (→ an altered sub-network) to predict the class labels for new samples



GenePEN - Approach

Idea: Cast the gene selection as an optimization problem, maximizing two quantities:

- the diagnostic prediction accuracy of the classifier
- connectedness of selected genes in the network

→ use a mathematical programming formulation (details on next slide):

$$\min_{w} \underline{loss(w)} + \underline{\lambda} \cdot \underline{penalty(w)}$$

loss-function (minimize error)   trade-off parameter   penalty-function (gene grouping)

→ Output: an optimized vector of feature weights ***w**:*

$\mathbf{w}_i \approx 0 \rightarrow$ gene i not selected

abs($\mathbf{w}_i$) large $\rightarrow$ gene is relevant for the prediction and well-grouped with other selected genes in the network

GenePEN – The loss and penalty functions

GenePEN objective function:

$$\min_{w} \underbrace{loss(w)}_{(1)} + \lambda \cdot \underbrace{penalty(w)}_{(2)}$$

- **(1)** the loss function is the expected logistic loss (smooth and convex → can be minimized efficiently):

$$loss(\underbrace{w}_{\text{gene weights}}, \underbrace{\nu}_{\text{offset parameter}}) = \tfrac{1}{n}\textstyle\sum_{i=1}^{n} \log\left(1+\exp(-\underbrace{y_i}_{\text{real labels}}\underbrace{(w^\top x_i+\nu)}_{\text{predicted labels}})\right)$$

- **(2)** the new convex penalty function penalizes the differences of absolute values (= measure of relevance) between the weights of neighboring genes/proteins:

$$penalty(\omega) = \sum_{i=1}^{p}\left[\sum_{j=1}^{p} \underbrace{A_{ij}}_{\text{adjacency matrix}} \left(|w_i| - |w_j|\right)\right]^2 + 2\underbrace{\Delta}_{\text{maximum network degree}} \|\omega\|_1^2$$

Previous penalty functions proposed

$\Omega(\mathbf{w}) = \|\mathbf{w}\|_2^2$	**Ridge** (Hoerl and Kennard, 1970) grouping but no sparsity
$\Omega(\mathbf{w}) = \|\mathbf{w}\|_1$	**Lasso** (Tibshirani, 1996) sparsity but no grouping
$\Omega(\mathbf{w}) = \|\mathbf{w}\|_2^2 + \alpha\|\mathbf{w}\|_1$	**Elastic Net** (Zou and Hastie, 2005) cannot capture local structure
$\Omega(\mathbf{w}) = \sum_{c\in\mathcal{C}} \alpha_c \|\mathbf{w}_c\|_2$	**Group Lasso** (Turlach et al., 2005) assumes non-overlapping groups
$\Omega(\mathbf{w}) = \mathbf{w}^\intercal\, \mathbf{K}\, \mathbf{w}$ (with $\mathbf{K}$ psd)	**graph kernel** (Rapaport et al., 2007) weight signs can introduce bias
$\Omega(\mathbf{w}) = \sum_{i<j} \max(\|w_i\|, \|w_j\|)$	**OSCAR** (Bondell and Reich, 2008) large weights can introduce bias

GenePEN – Application to Parkinson‘ disease data

- **Parkinson’s disease test dataset**: Microarray gene expression data from *post mortem* brain samples (*substantia nigra*) of 43 PD patients and 50 controls (Zhang et al., 2005)

- **Network data**: Human genome-scale protein-protein interaction network constructed from 80,543 public, direct physical interactions between 10,042 proteins.

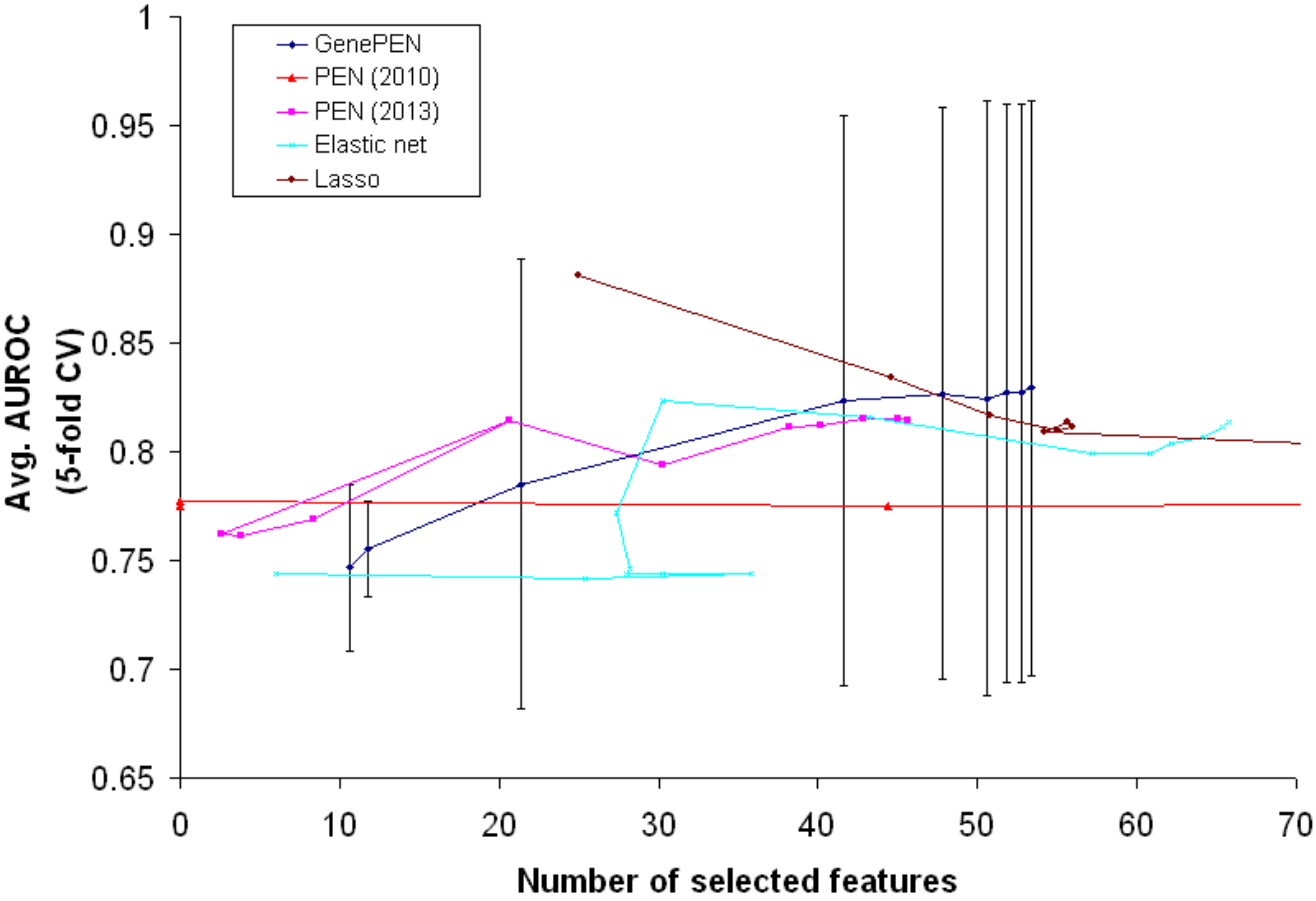
- **Comparison against other penalty functions**: The GenePEN penalty was compared against alternative penalty functions (Lasso, Elastic Net, Pairwise Elastic Net)

- **Evaluation criteria**:

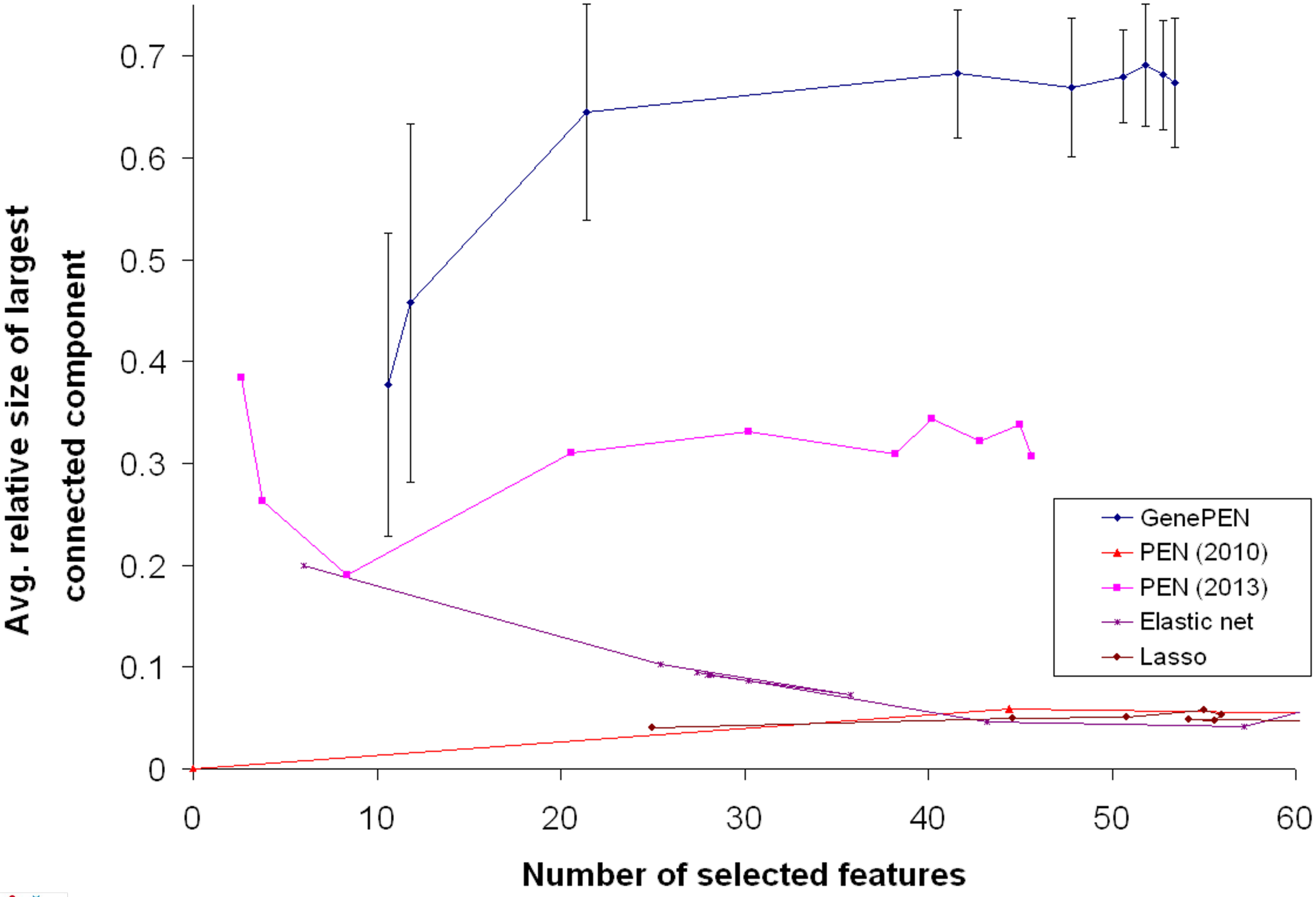
  → **cross-validated prediction performance**:
  avg. area under the receiver operating characteristic curve (AUROC) for different numbers of selected features

  → **cross-validated grouping of selected genes in the network**:
  avg. relative size of the largest connected component among selected features in the network

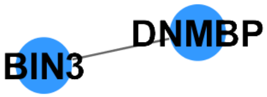
Comparison of AUROC performance



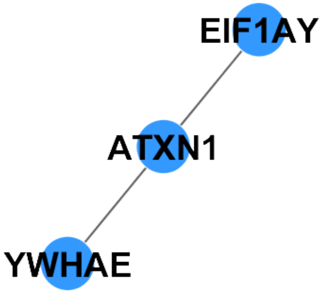
Relative size of largest connected component in network



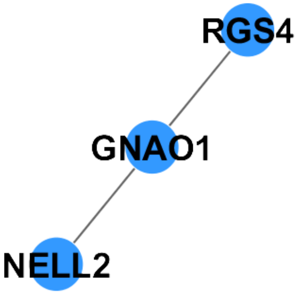
Comparison: Largest cluster for ~50 selected genes



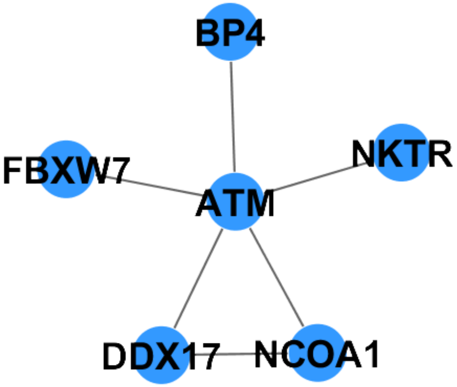
Lasso



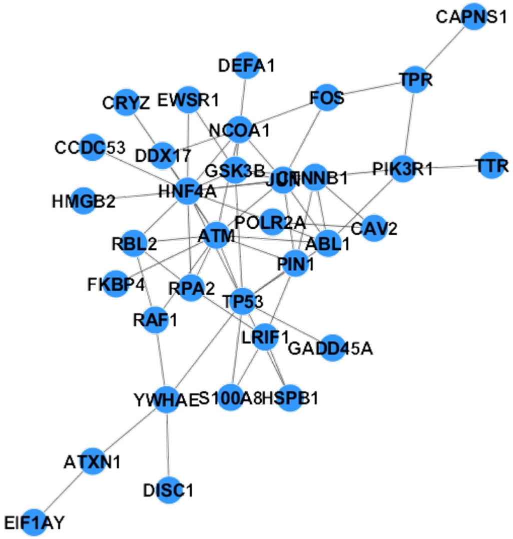
Elastic Net



PEN (2010)



PEN (2013)



GenePEN → cluster of 34 genes

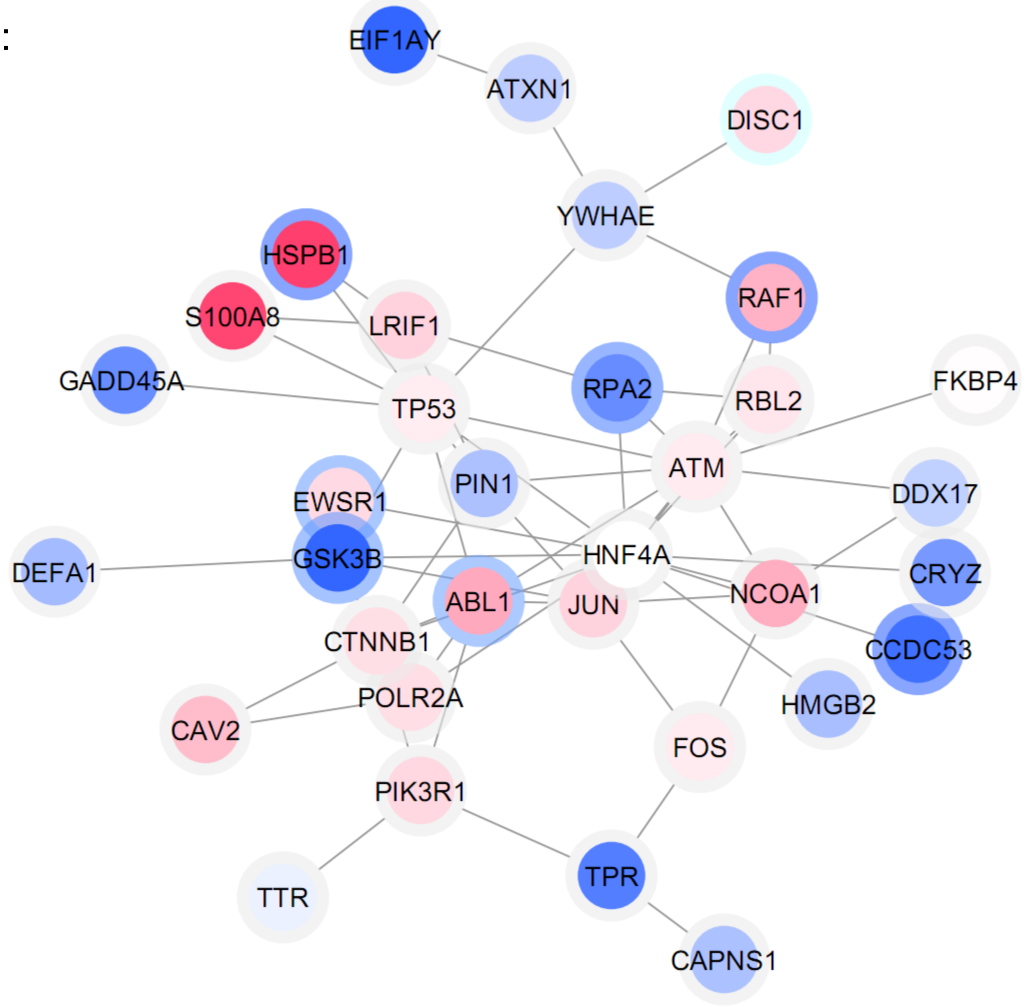
Biological results: PD-associated sub-network

Largest connected graph component identified on PD transcriptomics data:

- red = over-expressed in PD
  blue = under-expressed in PD
  node borders = individual statistical significance (from gray to blue with increasing significance)

- individually significant genes are significantly over-represented in the sub-network (p = 0.01)

- Pointwise mutual information (PMI) co-occurrence scoring of gene names and MeSH disease term "Parkinson's disease" in PubMed reveals enrichment of positive scores



Summary & Acknowledgements

- Integrating **prior knowledge** from molecular networks and pathways into omics data analysis can provide benefits in terms of model robustness and biological interpretability

- **GenePEN** discovers **discriminative sub-networks** for diagnostic sample classification and enables an interpretation of disease-associated molecular alterations at the network level

- On **Parkinson‘s disease transcriptomics data** GenePEN identifies predictive alterations in sub-networks which are enriched in individually significant genes and known PD-associated genes with positive PMI scores

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