A co-expression network analysis reveals homogeneous functional clusters and important genes related to a phenotype of interest

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Outline

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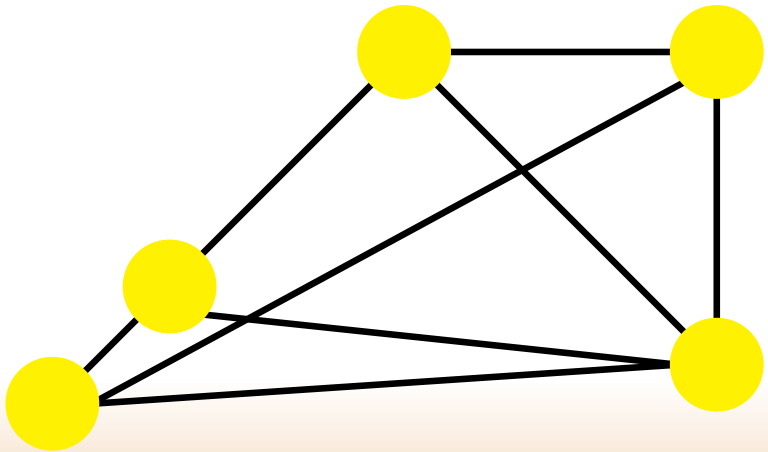
- **272 genes whose expression is (partially) under genetic control** were selected. Among them, only 2 are differentially expressed for pH.

Outline

From genes to genes network

Purpose: Detect and analyze the biological process in its whole.

What is a gene co-expression network?



nodes: genes

edges: “significant” correlation between gene expressions

Correlation and partial correlation

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- **H**: gene expressions, X, are distributed as $\mathcal{N}(\mu, \Sigma)$;
- **Quantity to estimate**: Partial correlations, i.e., $\pi_{ij} = \mathrm{Cor}(X^i, X^j | (X^k)_{k \neq i,j})$;

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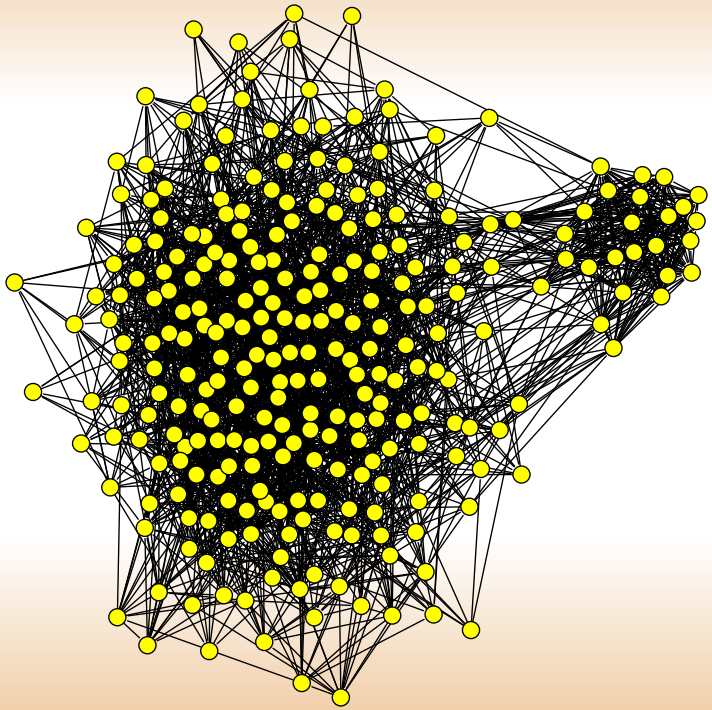
Use of "GeneNet" R package [Schäfer and Strimmer, 2005]: bootstrap estimation and Bayesian approach to test the significativity of the partial correlation.

Basic description of the co-expression network



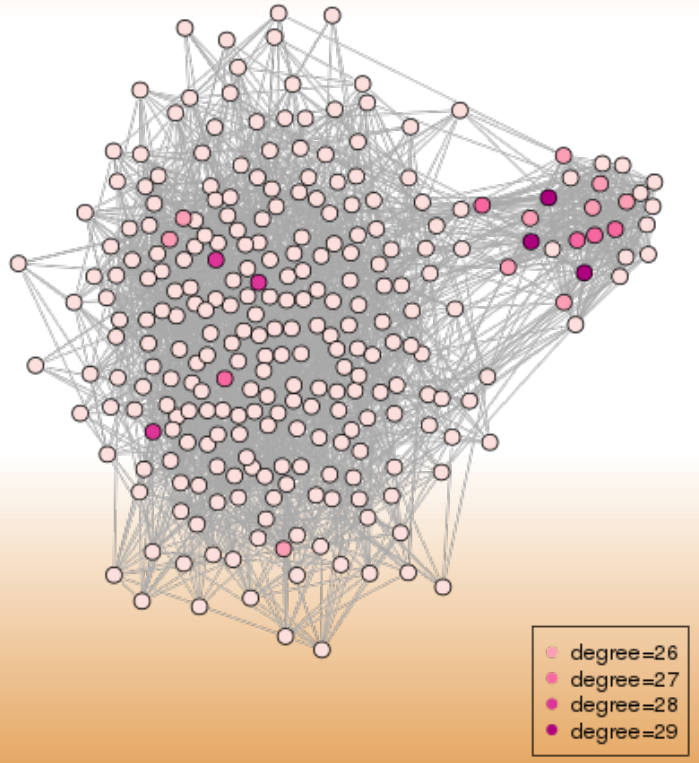
272 nodes (connected graph), density: 6.4 %, transitivity: 25.4 % (hence, probably a modular structure)

Outline

Key genes

Nodes degree: Number of links connected to a given node.

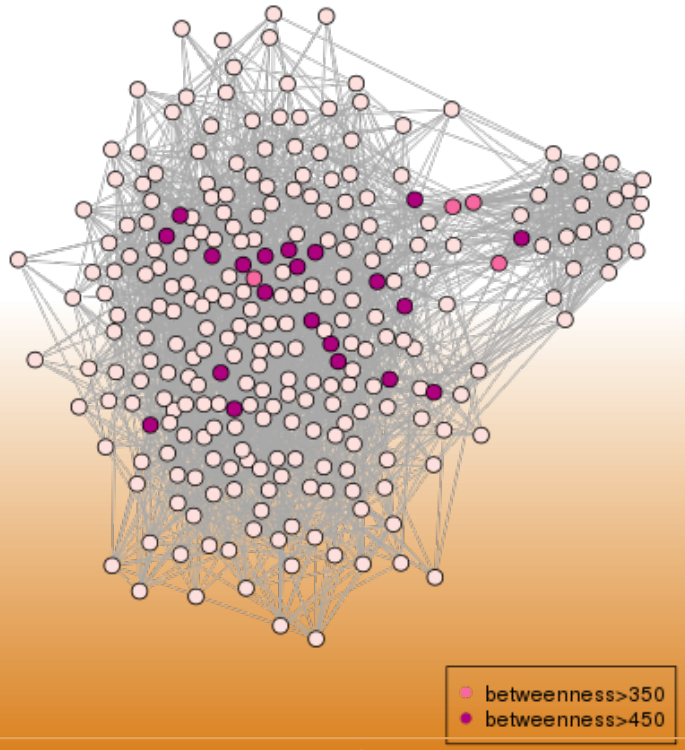
21 hubs (nodes with high degrees) identified



Key genes

Betweenness: Number of shortest paths between two nodes passing by a given node (measure of the importance of a given node to connect the graph)

25 genes with a high betweenness identified



Comments

From these two lists were found:

- **genes already known** to be involved in meat quality (biological validation);
- **annotated genes** that have never been related to meat quality (unexpected genes);
- **unknown genes** (not even annotated).

$\Rightarrow$ unexpected and unknown genes are good candidates for a deeper biological analysis.

Nodes clustering

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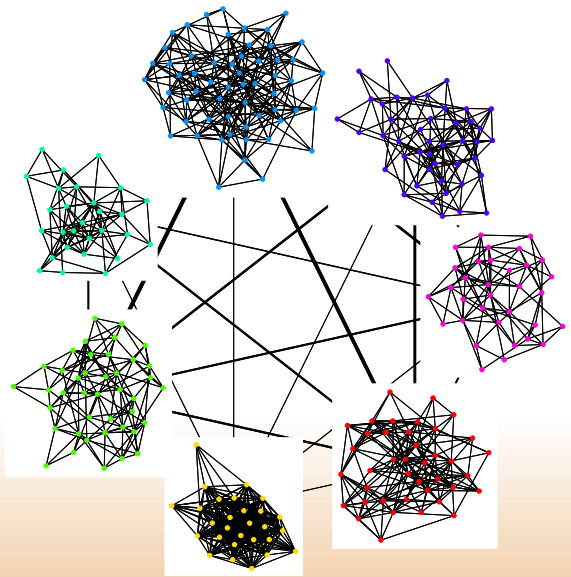
Methodology: Modularity optimization

$$Q = \sum_{i,j \in C_k} \left(W_{ij} - \frac{d_i d_j}{2m} \right)$$

with $d_i = \sum_l W_{il}$ and $m = \frac{1}{2} \sum_i d_i$ **[Newman and Girvan, 2004]** by simulated annealing (after a previous comparison of several methods and parameters).

Results

- **7 clusters** with 28 to 58 nodes;



Results

- **7 clusters** with 28 to 58 nodes;
- For annotated genes, at least 68% (but often more than 80%) of a given cluster, **belong to a single IPA network** (literature validation) $\Rightarrow$ assumptions for functions of unknown genes.

Superimposing additional information on nodes

Purpose: Study of the correlation between the network topology and a phenotype of interest.

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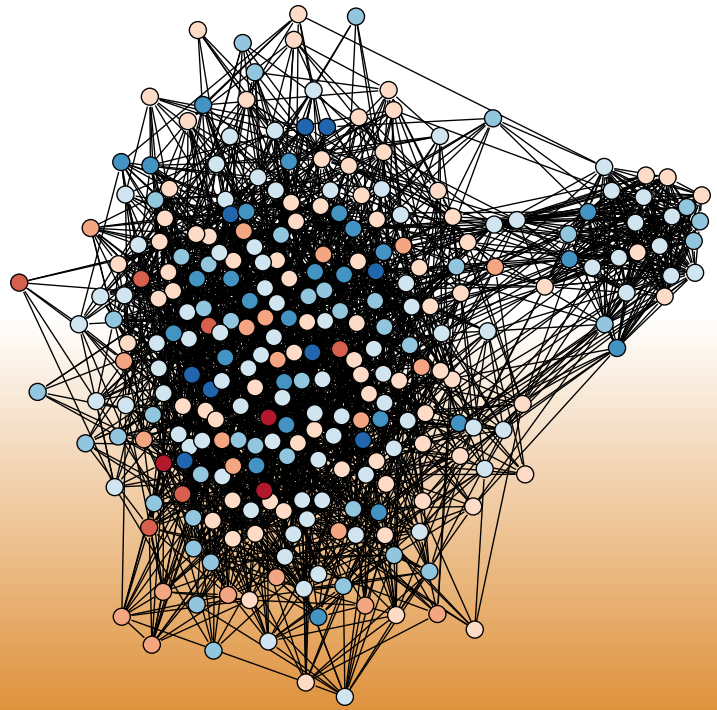
Data: Partial correlation between pH and gene expression.



Fist analysis of the relations between pH and network topology

[Laurent and Villa-Vialaneix, 2011]

- **Cluster 4** has a significatively higher correlation with pH than the other clusters;

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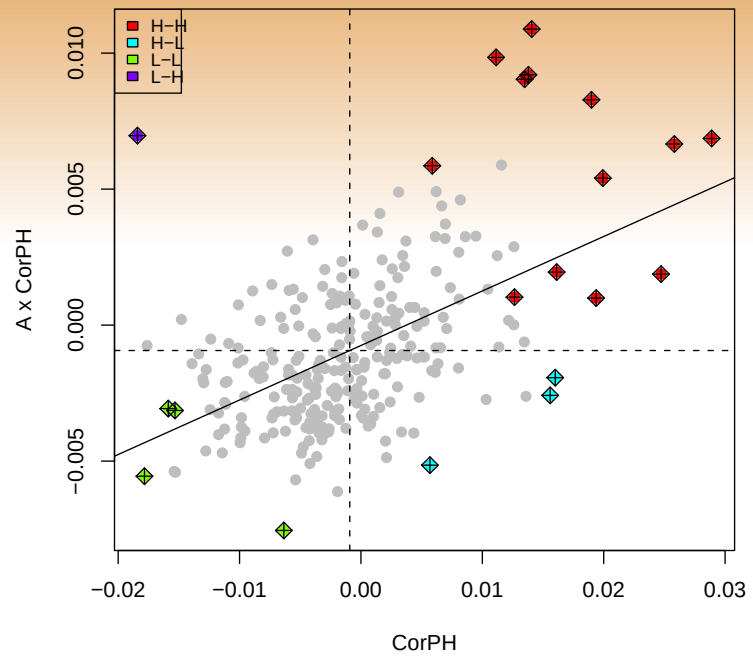
- **Cluster 4** has a significatively higher correlation with pH than the other clusters;
- Network auto-correlation of the labels can be assessed through Moran's I

$$I = \frac{\frac{1}{2m}\sum_{i\neq j} w_{ij}\bar{c}_i\bar{c}_j}{\frac{1}{n}\sum_i \bar{c}_i^2}$$

where $m = \frac{1}{2}\sum_{i\neq j} w_{ij}$, c_i is the label of node i (partial correlation with pH) and $\bar{c}_i = c_i - \bar{c}$ with $\bar{c} = \frac{1}{n}\sum_i c_i$.
Moran's I is significatively large: **network topology is related to partial correlation with pH**.

Moran's plot



Average values for partial correlation with pH in the neighborhood of a node in function of the partial correlation with pH for this node.

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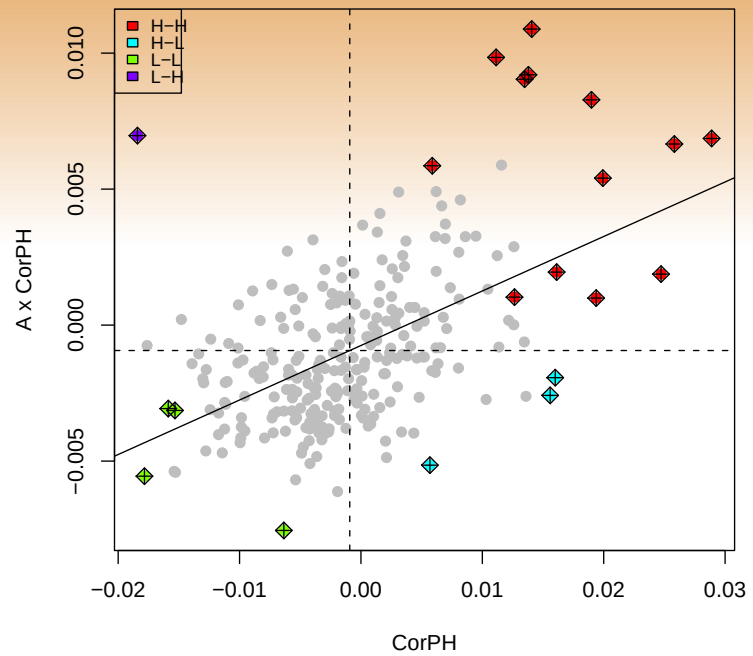

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Influential nodes can be extracted: most belong to cluster 4 and some of them are already known to be involved in meat quality (e.g., one gene involved in glycolysis and gluconeogenesis).

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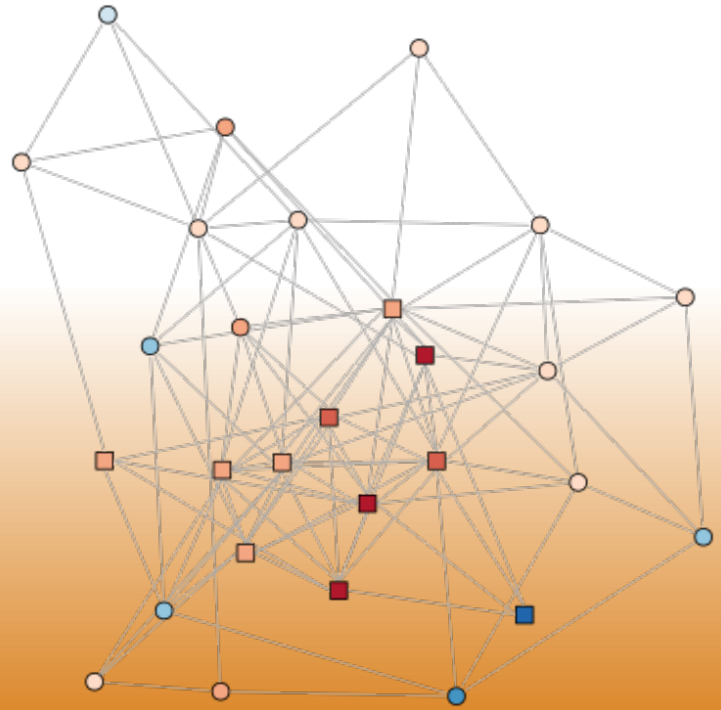

Conclusion

Statistical approaches were **validated by biological knowledge**:

- clusters are consistent with the literature (homogeneous biological functions);
- some key genes extracted from the analysis of the partial correlation with pH are already known to be involved in meat quality.

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Hence, **unexpected statistical results could provide insights about unknown genes** (their function, that they are possibly involved in meat quality...)

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