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ANALYSIS OF TGF- β SIGNALIZATION PATHWAYS THANKS TO TOPOLOGICAL AND SEMANTIC WEB METHOD

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CONTEXT

- TGF- β = Transforming Growth Factor β
 - necessary in healthy situation
 - deleterious role in fibrosis and cancer
- Pleiotropic effects of TGF- β are linked to the complex nature of its activation and signaling networks

BIOLOGICAL QUESTIONS:

Which pathways are cancer-specific?

Which mechanism is involved in the healthy \rightarrow pathological transition?

SIGNALIZATION MODEL

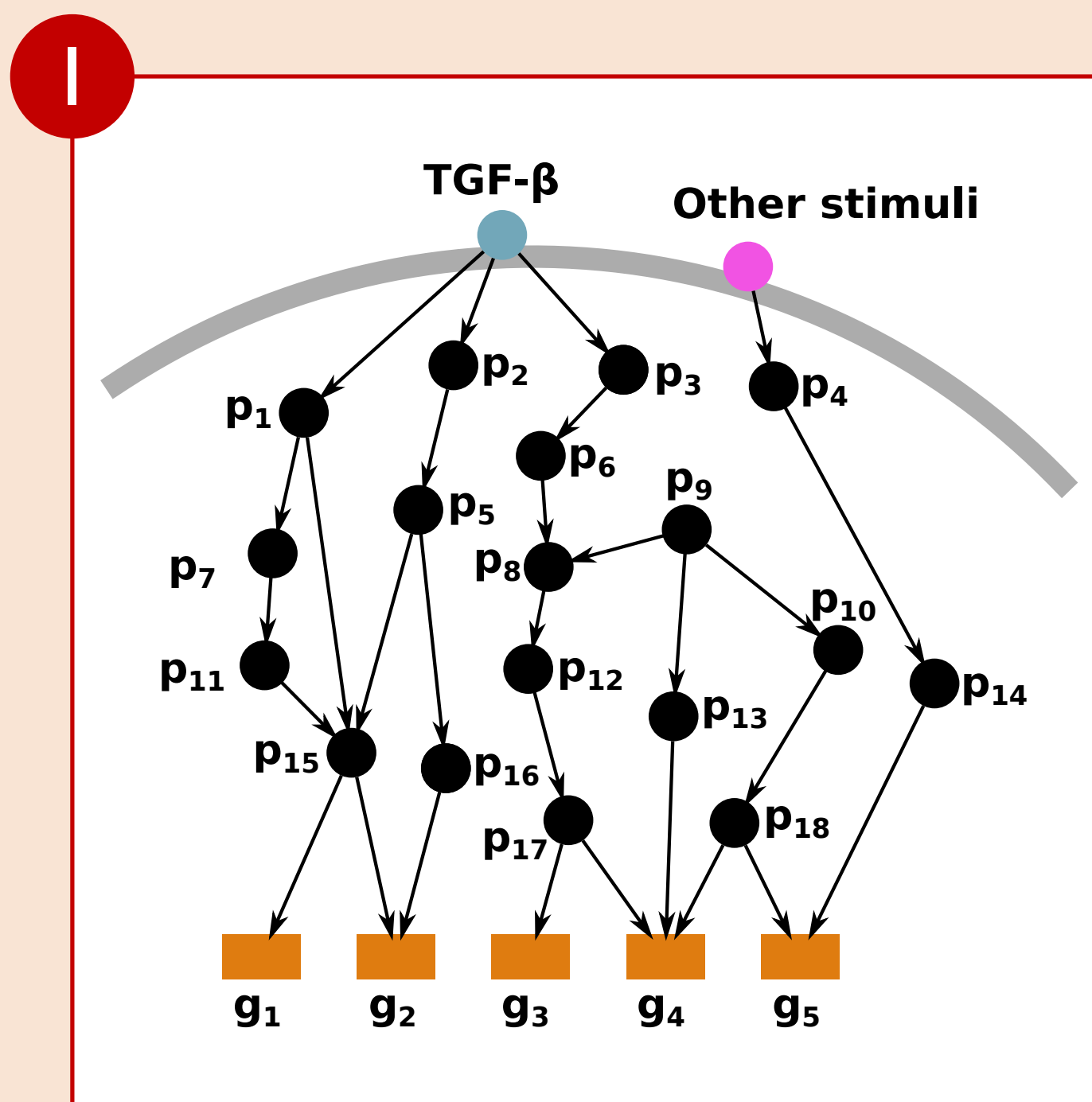
- Model of TGF- β signal propagation based on guarded transitions [Andrieux et al, 2014] represented in CADBIOM.
- Pathway Interaction Database (PID) transform into a single unified model of signal transduction

DATA ANALYSIS PROBLEM:

16,000 chains of reactions linking TGF- β to at least one of 159 target genes.

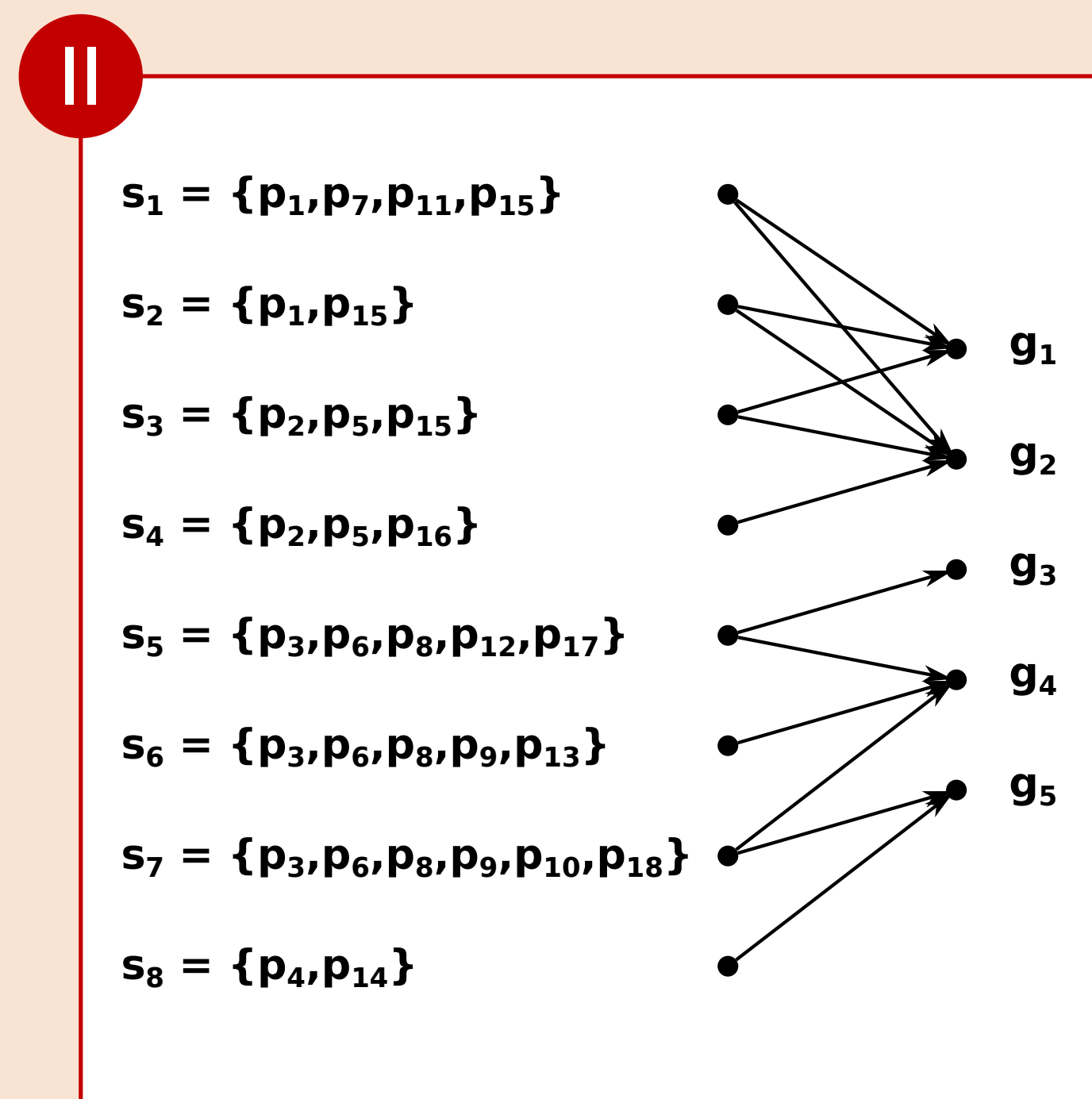
How to explore the combinatorial complexity of cell signaling?

ANALYSIS OF SIGNALING PATHWAYS : STEPS METHOD



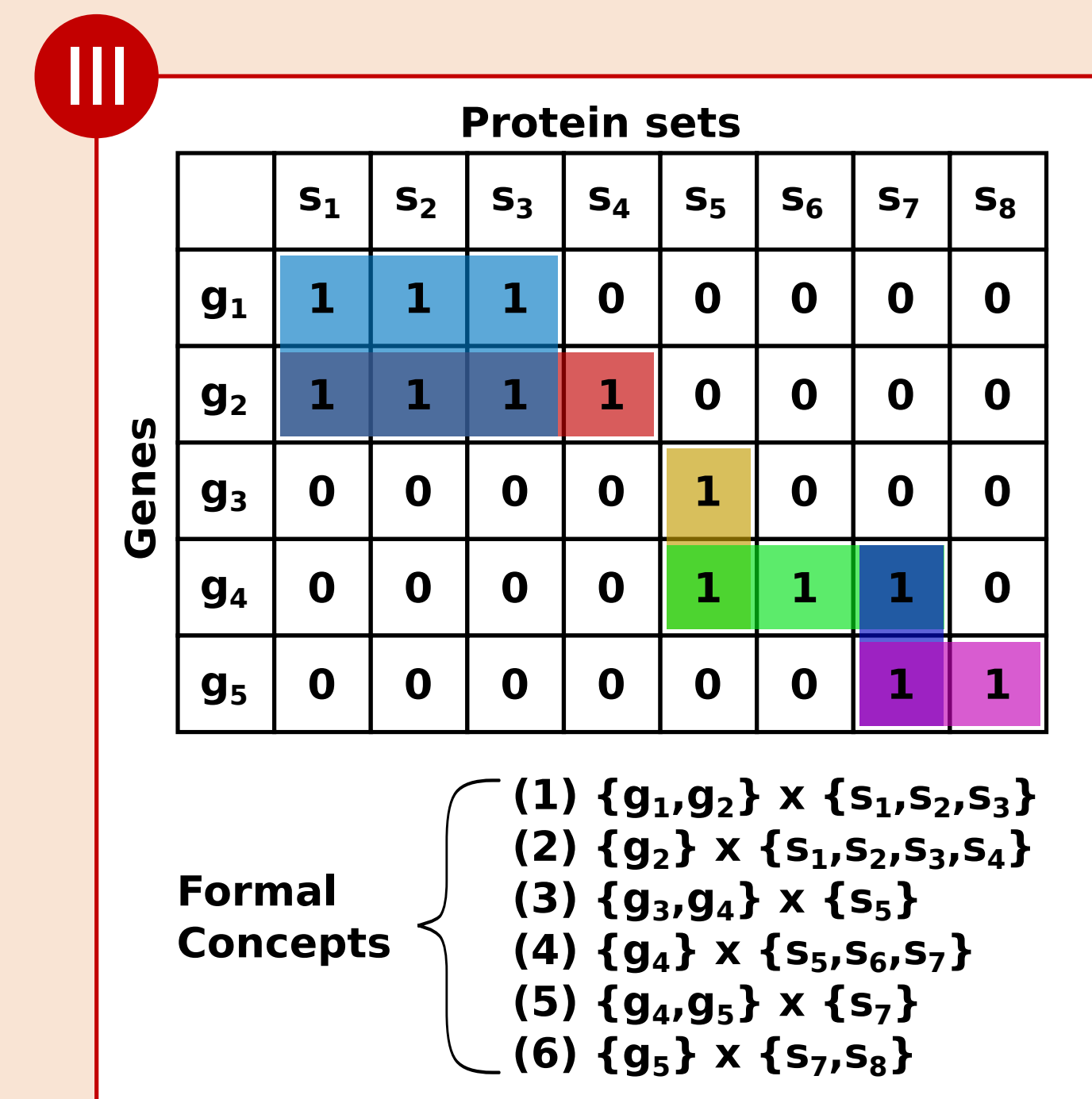
RAW DATA

- TGF- β signalizations influence some genes
- Other stimuli in addition to TGF- β



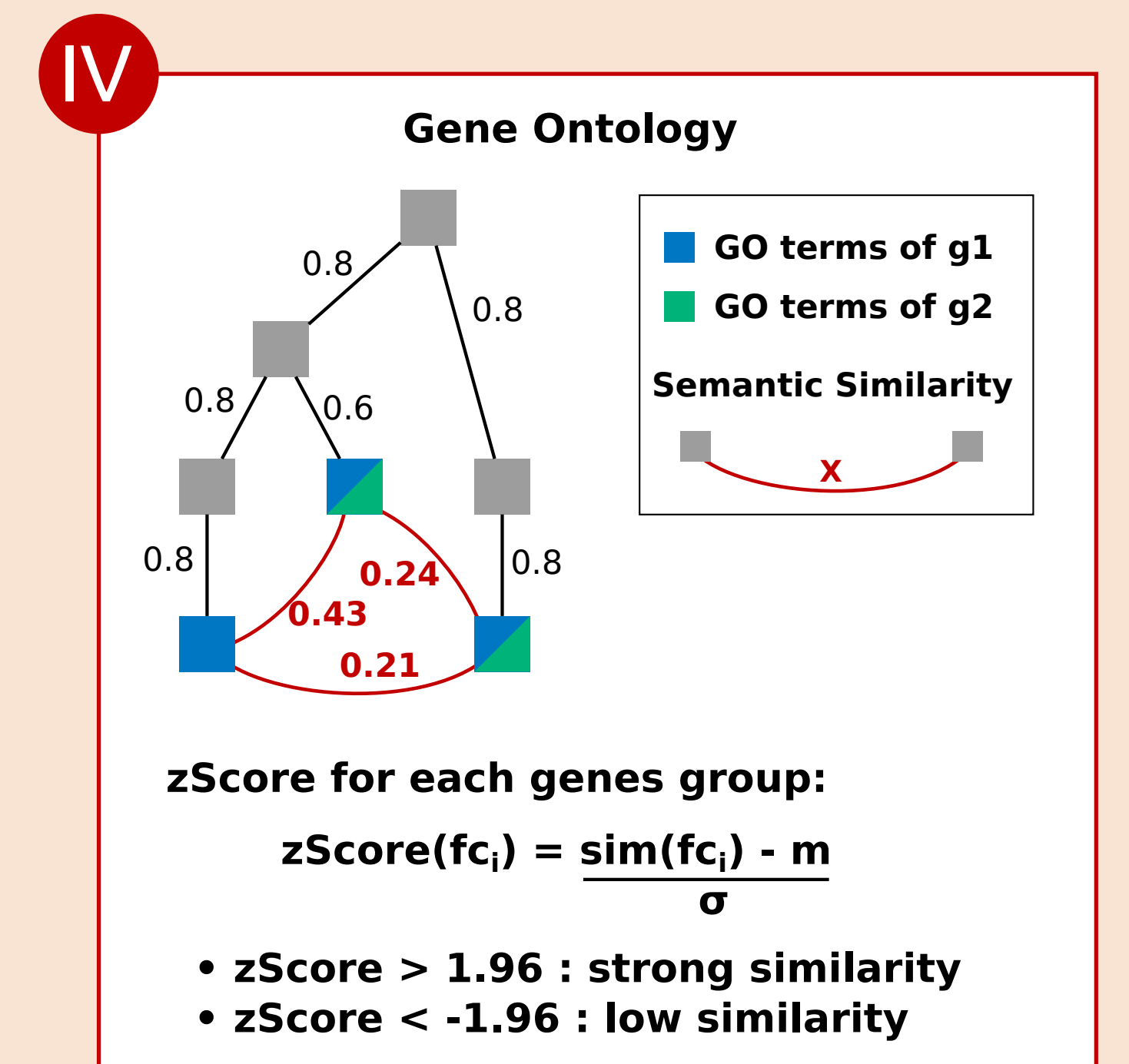
GENES INFLUENCED BY PROTEIN SETS

- Signaling pathway = proteins set
- Proteins set influence at least one gene



CLUSTERS OF SIMILAR GENES AND PROTEIN SETS

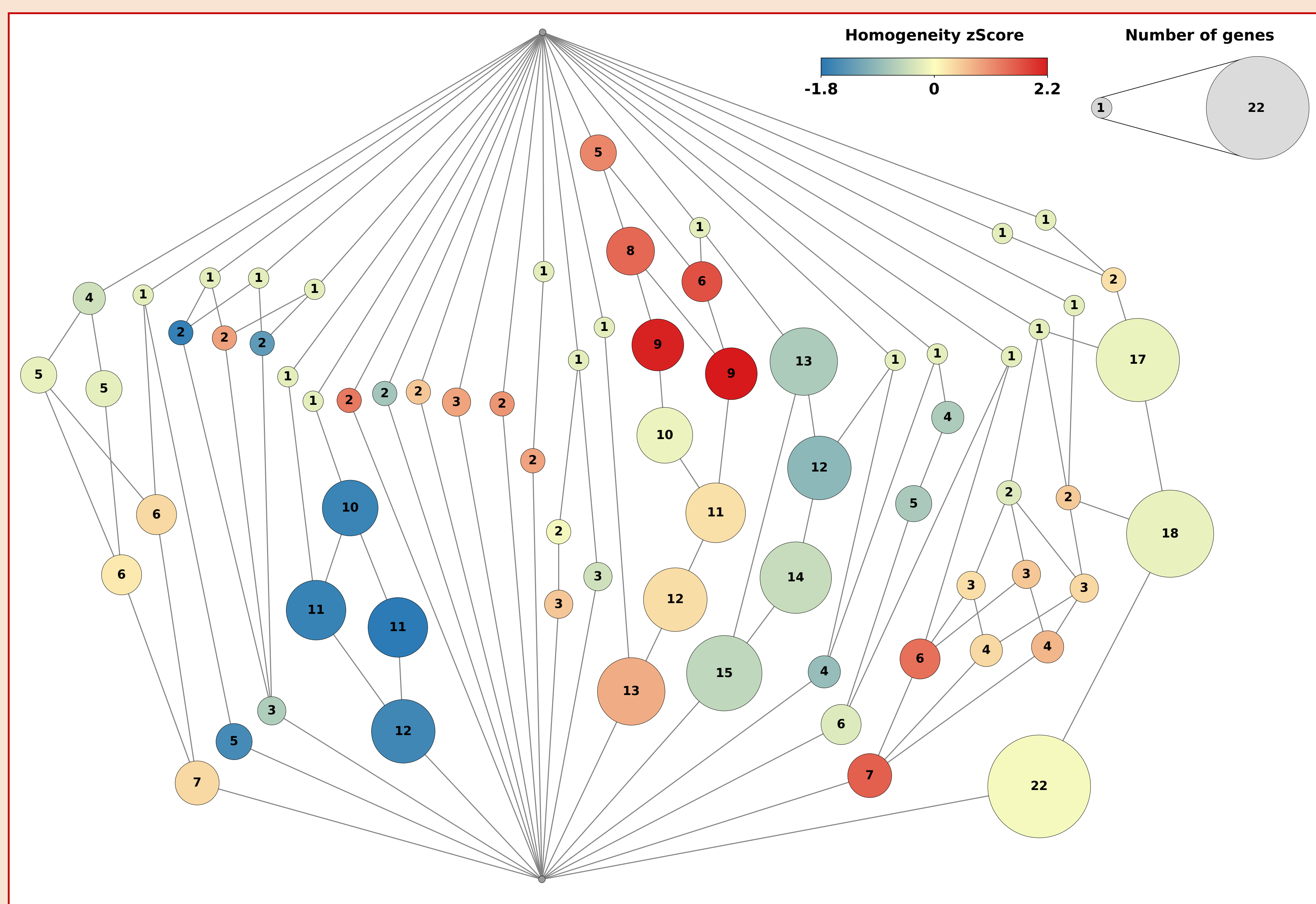
- Identify clusters of similar genes and protein sets with formal concept analysis
- Binary matrix
- Formal concepts = maximal bi-cliques



ASSESS CLUSTERS' BIOLOGICAL RELEVANCE WITH SEMANTIC HOMOGENEITY

- Formal concept homogeneity = zScore of similarity gene group
- Semantic similarity based on Wang measure [Wang et al, 2007]

RESULTS



Concept lattice. Nodes are formal concepts, two nodes are linked if one is included into the other.

DISCUSSION

- Some formal concepts are highly connected
- Gene clusters can have:
 - High homogeneity = genes similar influenced by same pathways
 - Low homogeneity = genes dissimilar influenced by same pathways
- Chains of gene clusters included into one-another indicates that some influence sets are specific to some gene subsets

IN PROGRESS

- Validate the method on small synthetic models
 - Improve the method to find better gene clusters
 - Integrate the overlap between proteins sets
 - Try different methods of clustering
- Compute the semantic homogeneity of protein sets
- Take into account the structure underlying gene sets
- Compute the stability of formal concepts

References:

- [Andrieux et al, 2014] Andrieux, G., Le Borgne, M., & Thérêt, N. (2014). An integrative modeling framework reveals plasticity of TGF-beta signaling. BMC systems biology, 8(1), 30.
- [Wang et al, 2007] Wang, J. Z., Du, Z., Payattakool, R., Philip, S. Y., & Chen, C. F. (2007). A new method to measure the semantic similarity of GO terms. Bioinformatics, 23(10), 1274-1281.

CONCLUSION

Model of TGF- β signal propagation

New method to analyze pathways:

- Topological analysis
- Clustering
- Biological relevance

Gene clusters influenced by same pathways with a biological relevance