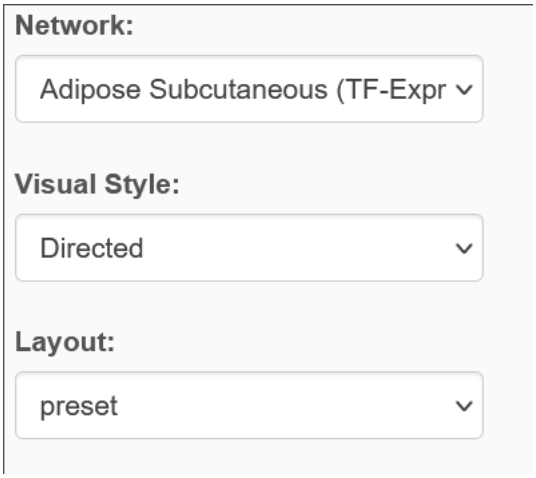
Tutorial

How to use the website?

This website provides two sets of networks:

1. Networks of co-regulated genes across tissues. Genes that are co-regulated across multiple tissues based on our published method. These networks are correlation-based and non-directional.
2. Regulatory cascades. In these networks, a variation in a TF is associated with variation in a gene expression, but the expression levels of the TF are themselves associated with a higher-level TF. These networks show cascades of regulation, where TFs could regulate other TFs, which in turn regulate gene expression. We provide two types of networks:
    1. Full networks of the TFs and regulated genes.
    2. To allow convenient browsing, we provide networks that show only the genes+TFs that are themselves regulated and the full networks, that show all TFs, including ones that were not directly regulate in our models.

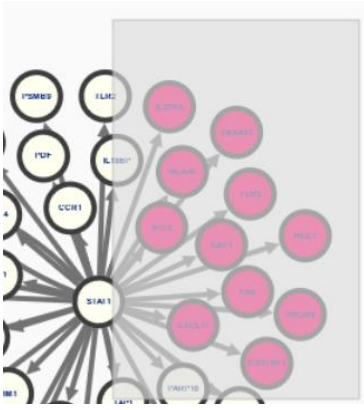
The networks were generated through Cytoscape and allow selection of the type of network (based on the type of model generated it – TF-Expression or TF-Binding) and for the regulatory networks based on the tissue it was calculated in.



The visual style allows different ways to visualize the nodes and edges in the network. The default one is pre-selected to reflect the best way to convey the information in the network but other choices are available.

The layout of the network allows using different algorithms that order the nodes and edges of a network.

- Selection of subset of nodes can be done by either holding SHIFT key while clicking them individually, or dragging a rectangle across the area of the nodes
- The nodes can be manually rearranged by dragging them holding the mouse left click.
- Zooming in and out of specific section of the network can be with the mouse scroll wheel, where the location of the mouse pointer is the section that will be zoomed-in.



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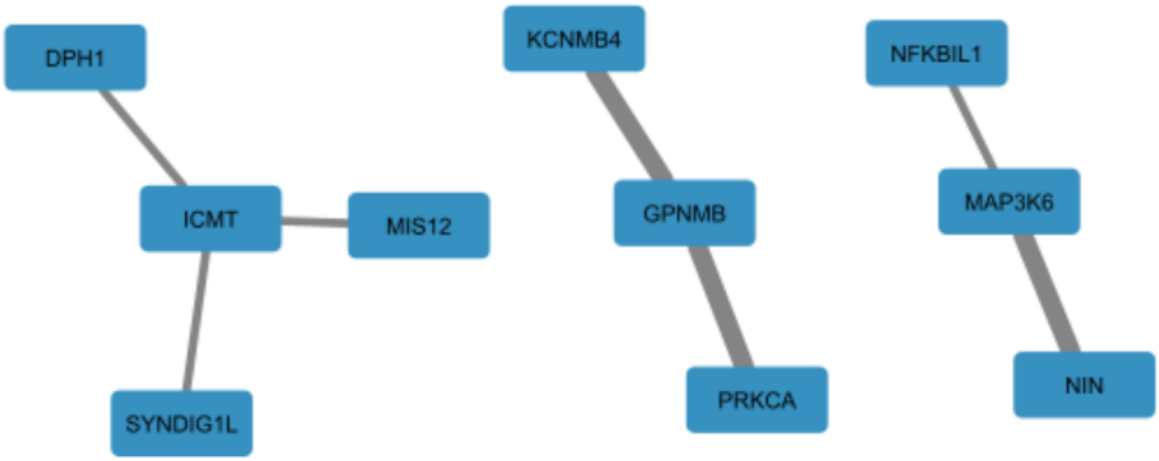
1. Co-regulated gene networks

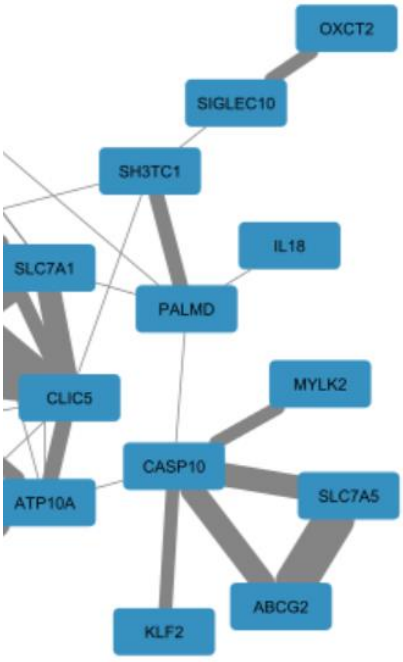
The co-regulation networks was computed across tissues. It includes genes that were modeled in at least three tissues and the tissue overlap between each gene pair has a Jaccard score of at least 0.5 and reached statistical significance (False discovery rate<0.05). Statistical significance of these co-regulated genes was computed using hypergeometric test and all p-values were corrected using Benjamini-Hochberg false discovery rate.

Use cases: potential use cases could be looking for gene modules that are co-modulated with relation to specific human phenotypes. One such example, also discussed in our paper, is examining the highest correlation across tissues, depicted here by line thickness. In the below figure, extracted from the TF-Binding model network, shows that the highest co-regulation across tissues involves the genes PRKCA, GPNMB and KCNMB4.



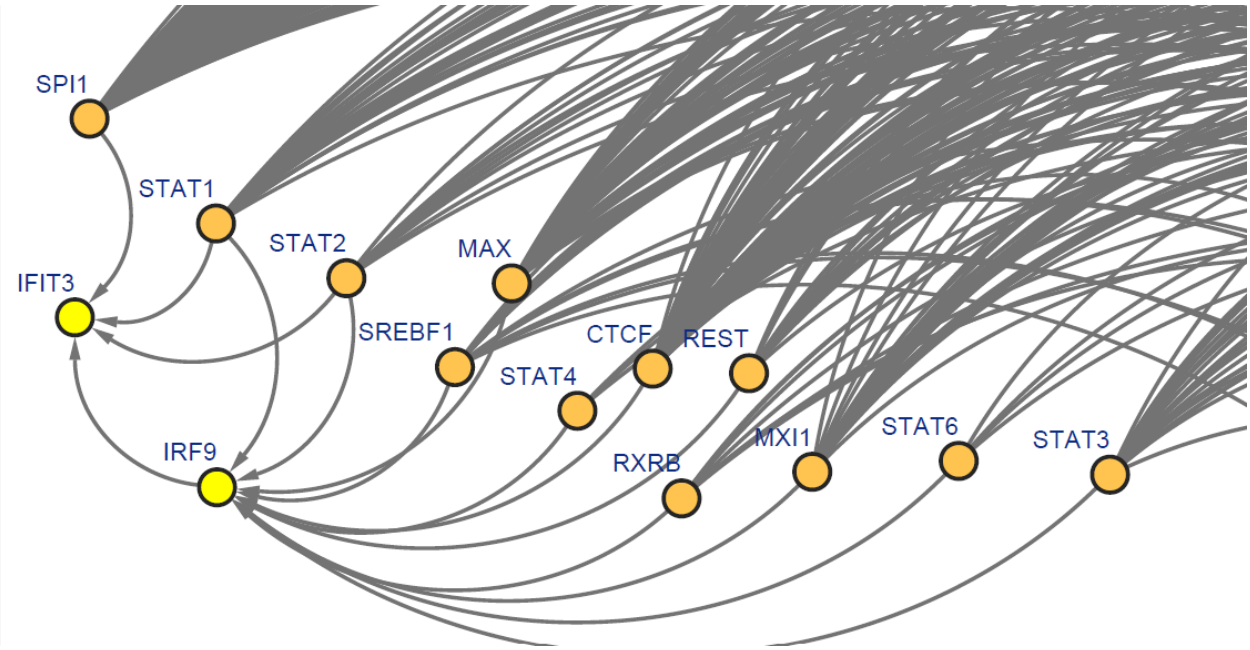
These genes were discovered across various brain tissues (cortex, hippocampus, hypothalamus and nucleus accumbens basal ganglia) and we demonstrated their association with neuronal activity and neurodegenerative disease like Alzheimer's Disease.

Another example from the TF-Expression model co-regulation can identify which modules are string and which are weaker (see excerpt of the network on the right). In this example, the module formed by SLC7A5, ABCG2, CASP10, MYLK2 and KLF2 (see right figure) form a strong co-regulation module and is only weakly associated with genes in other modules like PALMD or ATP10A.



2. Regulation cascades

Regulation cascades are identified when a gene's expression is modeled by the TFs in the model, and in turn, some of these TFs are also modeled by other set of TFs, forming regulation cascades in specific tissues. In order to enable easier viewing, we provide sub-networks that include only the TFs that are themselves modeled. In the figure below, this means only the genes in yellow and excluding the TFs modeling these genes in orange.



Use cases: Identifying possible mechanisms of both direct and indirect effects of regulation on specific biological processes. One example that is described in our paper is the possible co-regulation of IFIT and its TF IRF9 (shown in yellow in the above figure). IRF9 has the highest weight in the models of IFIT3 and is modeled in four tissues where IFIT3 is also modeled in several tissues like breast tissue. Recent studies have implicated IFIT proteins as prognostic markers to determine the clinical outcome of breast cancer while IRF9 is not only associated with the development of resistance to antimicrotubule agents in breast tumor cells, but is also reported as potential link to downstream mediators of IFN signaling to drug resistance in human cancers. Although STAT1 and STAT2 are not hit genes by themselves, TFs from the STAT family have established connections to breast cancer and skin (shown in orange in the figure).