Gene regulatory network

A gene (or genetic) regulatory network (GRN) is a collection of molecular regulators that interact with each other and with other substances in the cell to govern the gene expression levels of mRNA and proteins. These play a central role in morphogenesis, the creation of body structures, which in turn is central to evolutionary developmental biology (evo-devo).

GRNs obtained using Machine Learning techniques are often dense, whereas real GRNs are rather sparse. We use a Tikonov regularization inspired optimal L-curve criterion that utilizes the edge weight distribution for a given target gene to determine the optimal set of TFs associated with it. Our proposed framework allows to incorporate a mechanistic active biding network based on cis-regulatory motif analysis. We evaluate our regularization framework in conjunction with two non-linear ML techniques, namely gradient boosting machines (GBM) and random-forests (GENIE), resulting in a regularized feature selection based method specifically called RGBM and RGENIE respectively. RGBM has been used to identify the main transcription factors that are causally involved as master regulators of the gene expression signature activated in the FGFR3-TACC3-positive glioblastoma. Here, we illustrate that RGBM identifies the main regulators of the molecular subtypes of brain tumors. Our analysis reveals the identity and corresponding biological activities of the master regulators characterizing the difference between G-CIMP-high and G-CIMP-low subtypes and between PA-like and LGm6-GBM, thus providing a clue to the yet undetermined nature of the transcriptional events among these subtypes [1].

[1]

Mall R, Cerulo L, Garofano L, Frattini V, Kunji K, Bensmail H, Sabedot TS, Noushmehr H, Lasorella A, Iavarone A, Ceccarelli M. RGBM: regularized gradient boosting machines for identification of the transcriptional regulators of discrete glioma subtypes. Nucleic Acids Res. 2018 Jan 19. doi: 10.1093/nar/gky015. [Epub ahead of print] PubMed PMID: 29361062.

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