Constructing and analyzing disease-specific or developmental stage-specific transcription factor and miRNA co-regulatory networks

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TFmiR is a freely available web server for integrative analysis of combinatorial regulatory interactions between transcription factors, miRNAs and target genes that are involved in disease processes in human [1]. To better characterize the differential cellular processes at molecular level from a network perspective in normal and disease conditions in human and now also in mouse, we have extended the published version by various new features such as the construction of tissue-specific networks. Besides disease processes, the successor of TFmiR can now also be applied to identify regulatory motifs associated with the transitions between different developmental stages from the sets of genes and miRNAs provided by the user. One particular challenge in studying gene regulatory networks is to identify the main drivers and master regulatory genes that control such cell fate transitions. In addition to common topological measures and by considering tissue-exclusive genes, we reformulate this problem as an optimization problem of computing a Minimum Connected Dominating Set (MCDS) for directed graphs. MCDS is applied to the well-studied gene regulatory networks of E. coli and S. cerevisiae and to a pluripotency network for mouse embryonic stem cells. The results show that the MCDS captures most of the known key player genes identified so far in the model organisms. Moreover, this method suggests an additional small set of transcription factors as novel key players for governing cell-specific gene regulatory networks. This set can also be investigated with regard to diseases. [1] Mohamed Hamed, Christian Spaniol, Maryam Nazarieh and Volkhard Helms, Nucleic Acids Res. 43: W283-W288 (2015).