In this work, we have presented scPADGRN, a novel DGRN inference method using time-series scRNA-seq data. scPADGRN shows advantages in terms of accuracy, robustness and fast convergence when implemented with thePADMMalgorithm for network inference using

simulated datasets.

In real scRNA-seq data applications, scPADGRN can be used to visualize gene-gene interactions among genes involved in the same biological process or KEGG pathway. These regulation relationships may either persist or disappear.

To quantify network differences, a quantitative index called DGIE has been presented. The DGIE score measures the communication ability of a certain set of genes. At the local level, we have computed the DGIE scores of processes or pathways that are directly related to ES cell differentiation. The decreasing tendency of the DGIE scores indicates that the differentiation functions of ES cells are most active initially and may gradually fade over time. At the global level, the DGIE scores of the three investigated datasets all show the same increasing tendency,indicating that the communication strength of the known contributing genes increases from ES cells to terminally differentiated cells. We have identified a set of genes responsible for changes in the DGIE scores during cell differentiation for each of the three single-cell datasets.

Our results affirm that single-cell analysis based on network inference coupled with quantitative computations can be applied to infer the activity states of gene functions in the process of differentiation from ES cells to terminally differentiated cells, thus potentially revealing key transcriptional regulators involved in cell differentiation and disease development.

In summary, our work provides three main contributions. First, we propose a new method of inferring DGRNs using scRNA-seq data. Second, a quantitative index, DGIE, is proposed to measure the communication ability of a certain set of genes in a DGRN; this index can reflect the activity states of functions in which these genes play a role. Third, key regulators of biological processes can be identified based on the DGIE scores.