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RECONSTRUCTION AND MODULAR RESPONSE ANALYSIS OF INTRACELLULAR TRANSCRIPTIONAL NETWORKS

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ABSTRACT

Human cell contains around 20 thousand genes, and a change of transcription level of each gene can potentially change expression levels of all other genes. Thus, genes in human cells form a regulatory network which is responsible for the cell's behaviour. Current single-cell high-throughput technique, called perturb-seq, allows targeted perturbing expression levels of hundreds of genes and measured genome-wide transcriptional responses. Such data, being very informative, suffers from a number of essential problems, such as sparsity (drop-outs in measured data), noise, and inability to estimate extent of perturbation for some genes.

The Modular Response Analysis (MRA) method was specifically developed to infer the structure of the network from dense and high-quality perturbation data. In present work we have developed a pipeline to adapt MRA for perturb-seq data. We inferred regulatory networks for a numberof perturb-seq datasets, and analysed statistical properties of inferred networks. We have found that the importance of nodes and edges in the network is following lognormal or power-lognormal distributions that give us insight into the mathematical framework (differential equations) governing signal propagation within the network. Interestingly, the nodes that exert the highest impact on activity of all other nodes, tend to be the least affected by activity of other nodes, suggesting hierarchical structure of intra-cellular signalling. Clustering of MRA-predicted responses suggests that dynamics of inferred networks can be described as mutual inhibition between clusters of mutual co-activation. We assume that such clusters generate multiple steady nodes, and their basins of attraction are separated by multiple saddles.

In my talk, I'll show how applying MRA to perturb-seq data opens new avenues for research of dynamics of intra-cellular regulatory networks and I'll raise the number of open questions that our group is working on with a view on potential scientific collaboration.