Protein interactions differences between seniors and adults across human tissues

Rotem Shpringer

Advisors: Prof. Esti Yeger-Lotem, Prof. Michal Ziv-Ukelson

Introduction: Proteins, the main building blocks of living cells, carry out their functions by interacting with other molecules and particularly with other proteins. The set of interactions between proteins is typically represented as a network, where nodes correspond to proteins and edges correspond to their interactions. The Yeger-Lotem lab recently developed a method for differential network analysis, DiffNet, which quantifies changes in protein interactions that occur between tissues [1]. In my project I adapted the DiffNet tool to analyze changes in protein interactions that occur during aging.

Methods: We created an up-to-date network of all known interactions between human proteins, by using the MyProteinNet web tool [2]. The network included 380,612 interactions between 18,979 genes. To identify changes that occur during aging, we used transcriptomic data gathered by the GTEx consortium [3]. We used data sampled from donors aged 20-39, which we termed adults, and donors aged 60-89, which we termed seniors, across 48 different tissues. We then tailored the DiffNet approach to analyze interaction differences between seniors and adults per tissue. Specifically, median gene expression was computed per gene for both seniors and adults. The weight of an interaction in adults or seniors was set to the sum of the medians of the genes involved. The differential weight per interaction was set to the difference between interaction weights in seniors versus adults.

Results: We created a weighted differential network containing 16,449 expressed genes and 287,090 interactions per tissue. In order to identify the tissues that are most altered during aging, we focused on the top 1% most upregulated interactions in seniors, and the top 1% most upregulated interactions in adults. We found that in total, brain sub-regions and cervix were most altered in aging. Interactions that were differentially upregulated in brain cortex of seniors were enriched for regulation of immune system process (p-value: 1.81E-26), while interactions that were differentially upregulated in brain cortex of adults were enriched for negative regulation of cell death (p-value: 9.45E-10). In the future, we can use these networks to find genes that modulate aging and diseases across tissues.

Tools: To enable biologists and bioinformaticians to study changes that occur during aging, we created the AgeNet web-server (http://netbio.bgu.ac.il/agenet/). The server was implemented in Python by using the Flask framework with data stored on a MySQL database. The website client was programmed using the ReactJS framework and designed with Semantic-UI. The network view is displayed by the cytoscape.js plugin.

References: