Revealing aging mechanisms from ensemble gene network inference methods*

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Abstract—The increasing number of sparsely and unevenly sampled gene expression experiments in aging research pose significant constraints in gene network inference. In addition, the inconsistency in predictions among gene regulatory network methods hampers the identification of true biological structure. Recent approaches show that ensemble predictions derived from community-based methods are more accurate and provide truly testable hypotheses. Such ensemble strategies combined with multiple aging datasets establish a robust cost-effective way for unraveling cross-tissue aging mechanisms and exonerate the need for refined microarray design.

Over the last years, a substantial number of methods provided novel insights at different molecular aspects of aging with the use of systems biology network-based approaches. The decline in cellular function during aging is the cumulative result of changes in the expression level of a number of genes. Towards this orientation, the construction of Gene Regulatory Networks (GRNs) plays a prevalent role in the system modeling of interactions and regulations among genes. However, the choice of the network inference method still remains challenging, since recent studies have shown that no single method performs optimally across diverse data. For this reason, we propose the integration of predictions from multiple methods, since it has been proved to lead to more confident networks [1].

We downloaded two mouse gene expression datasets from GEO database with accession numbers GSE9902 (heart) and GSE99005 (liver). We retained only the male young and old mouse samples (4740 genes in total) and discarded the middle-aged ones. On second level, we applied three well-known GRN algorithms, namely ARACNE [2], MRNET [3] and CLR [4], on young and old samples separately in both experiments. The size of the resulted networks ranged between 2.1-3.3 × 10^6. Additionally, in order to recover the cross-tissue mechanisms, we retained the overlapping networks between experiments in each state separately and ended up with 421750 (young) and 461418 (old) interactions. We examined the performance of the final network (in each state separately) compared to the single networks with regard to experimentally validated interactions. For this, we employed the available mouse protein–protein and protein-DNA interaction data. The high performance (measured with F-score metric) of the final network proves that the community-based strategy manages to reduce the network complexity without derogating from the true biological structure.

Interestingly, the hub genes (with degree above 150 relations) in young state were highly enriched (P-value < E-10) in the GO terms “metabolic process” and “response to stress”, whereas in old state were enriched in “gene expression”, “cell cycle” and “cellular biosynthetic process” terms. This observation indicates that different processes take over control during aging, which is partly explained by the fact that certain hub genes lost their topological status in the comparative state (Fig. 1).

![Figure 1. Hub age-related genes](image)

REFERENCES