Studying microRNAs using a network based systems biology approach: inferring network, predicting functions, visualizing and scoring microRNA data.

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A central dogma of molecular biology used to be that the flow of genetic information follows a ‘no way back’ from DNA to messenger RNAs (mRNAs) to proteins. The situation is far from being that simple. Here we focus on microRNAs, which are 19-24 base pair non-coding RNAs that regulate post-transcriptionally protein coding genes through specific binding to their mRNA targets. MicroRNAs are predicted to target multiple protein coding genes while at the same time, most protein coding genes are predicted to be the target of multiple microRNAs. As a result, we have inferred a human microRNA network in which a microRNA is a node, and two nodes are linked together if they share a given number of common targets.
The first 11 hubs, having more than 50 neighbors, form two dense subnetworks which we termed ‘assorted clubs’. We performed Gene Ontology enrichment on the shared targets for each club. The first club was predicted to regulate the transcription / translation machinery, and the second club to regulate signaling through small GTPases. The robustness of the approach was assessed by reproducing the predictions using a different algorithm to predict mRNA targets of microRNAs. We further experimentally validated the role of the 3 microRNAs of the second club, namely hsa-miR-612, hsa-miR-661 and hsa-miR-940. All of them led to a clear modification of the cytoskeleton organization after over-expression in cells. Furthermore, we identified a putative oncogenic role for miR-661 while the other two were implicated in tumor suppression.
Interestingly, the microRNAs connected to only one of the clubs shared its main gene ontology enrichment, whereas microRNAs connected to both clubs showed no clear enrichment. This particular network topology led us to propose a more general model of gene expression in which a microRNA network is incorporated.
Finally, we are currently developing a web interface to overlay microRNA data onto the associated network. The interest of this approach lies in the fact that neighbor microRNAs tend to have similar expression. Additionally, we are currently developing

a scoring method based on Markov random fields (MRF) to incorporate the network information together with other microRNA wide data.