

# Characterization of microRNA-Regulated Protein-Protein Interaction Network

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## Introduction

Protein-protein interactions are critical to most biological processes. Available high-throughput experiments on protein-protein interactions allow us to build the interaction network giving more insight [1]. MicroRNAs (miRNAs) regulate the protein encoding genes at the post-transcriptional level [2]. However, the relationship between protein-protein interaction network and miRNA regulation is still not clear. Investigating the relationship will help us understand how miRNAs influence the protein interaction network.

## Materials and Methods

Protein interaction networks can be characterized by topological properties such as degree (number of interacting partners per node), clustering coefficient, betweenness centrality, closeness centrality, and characteristic path length (average of shortest paths between nodes). Statistical analysis was performed by comparing the topological features of miRNA-regulated proteins with randomly selected proteins in the network.

To analyze the role that individual miRNAs play in the human protein interaction network, we obtained interaction data from the Human Protein Reference Database [3], and used the predicted miRNA targets from TargetScan [4] to perform the analysis.

## Results

A summary of the analysis results is listed in Table 1. Our analysis shows that target genes of individual miRNAs tend to interact with more proteins than other proteins and have higher betweenness centrality (Figure 1). This indicates that many of miRNA-targeted genes are network hubs and bottlenecks. When these genes are repressed by individual miRNAs, they may consequently affect a large amount of interacting proteins. Another interesting result is that the characteristic path length between the target genes of same miRNAs is significantly shorter, implying that the target genes of individual miRNA are closer to each other.

For the subnetworks formed by those proteins regulated by one miRNA, termed as L0 networks, the average density is greater than the density of whole network. We further extended these subnetworks by adding their interacting neighbors, noted as L1 networks, which show even higher average density. To investigate whether these subnetworks form any modules, we used the term ‘in-degree’ of a node to represent the number of its within-subnetwork connections, and ‘out-degree’ for its outside-subnetwork connections [6]. The average ratio of in-degree to total degree of L0 networks is quite small, implying that the proteins regulated by the same miRNA may not form a module. However, L1 networks exhibit sig-

Table 1: Summary of topological properties and their  $Z$ -scores.

	All	L0 networks			L1 networks		
	Mean	Mean	$\langle Z \rangle$	$p$ -value	Mean	$\langle Z \rangle$	$p$ -value
Degree	7.46	10.87	2.62	0.0132	21.25	29.48	0
Betweenness	$3.74 \times 10^{-4}$	$3.99 \times 10^{-4}$	1.87	0.0493	0.0015	21.91	0
Closeness	0.2577	0.2551	-0.23	0.4550	0.2671	2.29	0.0098
Clustering coefficient	0.1153	0.1152	0.04	0.4589	0.1111	-0.27	0.3926
Characteristic path length	4.27	3.92	-3.19	0.0004	3.30	-25.97	0
Density	$9.02 \times 10^{-4}$	0.0023	3.24	0.0071	0.0141	75.71	0
In-degree ratio	N/A	0.0311	2.13	0.0237	0.4480	35.82	0
Modularity $Q$	N/A	0.0013	0.67	0.2171	0.1907	92.38	0

nificantly higher in-degree ratio. Furthermore, we calculated their ‘modularities’ ( $Q$ ) [5] and found that the average modularity of L1 networks is also much higher than random subnetworks. Although proteins directly regulated by individual miRNA may not form a network module themselves, the miRNA-target genes together with their interacting neighbors show significantly higher density and modularity.

## Conclusion

We have performed analysis to elucidate the global correlation between miRNA regulation and protein-protein interactions in human. By selectively targeting the hub proteins and bottleneck proteins, miRNA may regulate the protein interaction network in a wider scope. As the target genes and their interacting neighbors may form functional modules, miRNA could influence specific biological functions through regulating a smaller number of selected genes. Our findings provide possible mechanisms of how miRNA may regulate the protein interaction network.

## References

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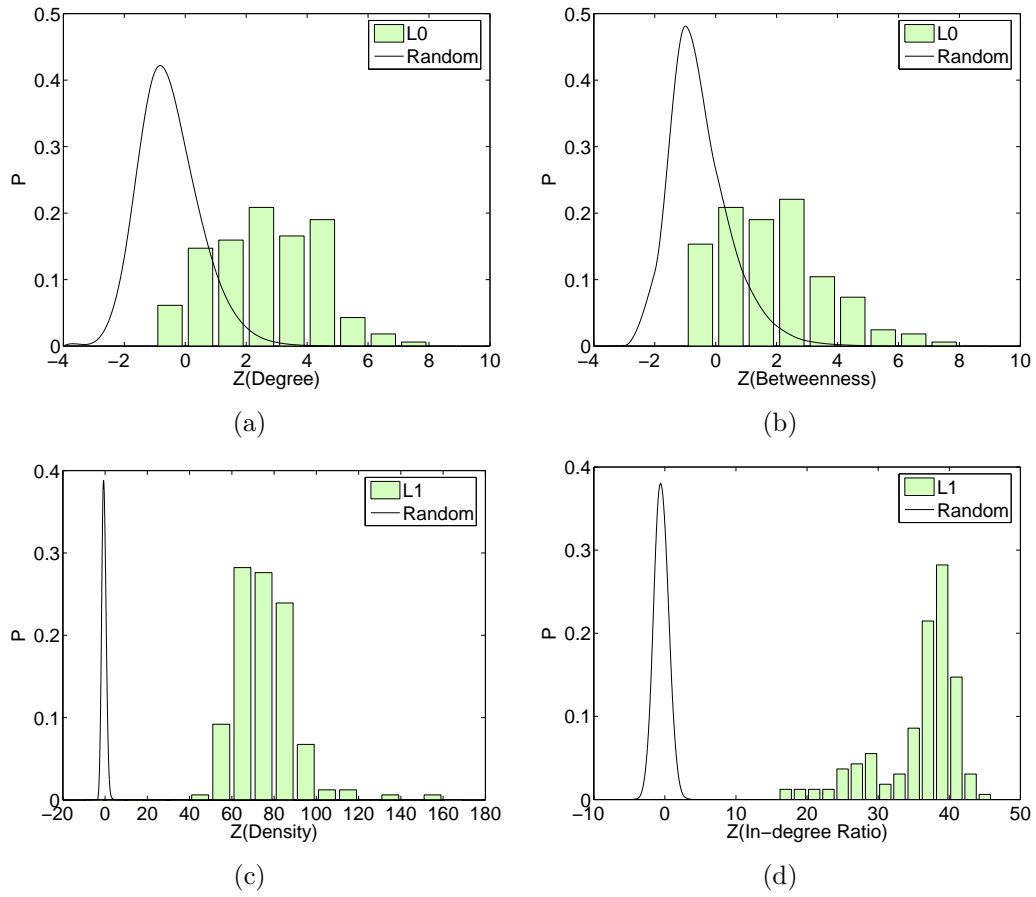


Figure 1:  $Z$ -score distributions of (a) degree of L0 networks, (b) betweenness centrality of L0 networks, (c) density of L1 networks, and (d) in-degree ratio of L1 networks.