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Evidence for the relationship between the regulatory effects of microRNAs and attack robustness of biological networks

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ABSTRACT

It has been previously suggested that microRNAs (miRNAs) have a tendency to regulate the important components of biological networks. The goal of the present study was to systematically test if one can establish a relationship between miRNA targets and the important components of biological networks (including human protein-protein interaction network, signaling network and metabolic network). For this analysis, we have studied the attack robustness of these networks. It has been previously shown that deletion of network vertices in descending order of their importance (e.g., in decreasing order of vertex degrees) can affect the network structure much more considerably. In the current study, we introduced three miRNA-based measures of importance: "miRNA count" (i.e., the number of miRNAs that regulate a given network component); average adjacent miRNA count, "AAmiC" (i.e., the average number of miRNAs regulating the targeted components adjacent to a given component); and total adjacent miRNA count, "TAmiC" (i.e., the total number of miRNAs regulating the targeted components adjacent to a given component). Our results suggest that "miRNA count" is only marginally capable of locating the important components of the networks, while TAmiC was the most relevant measure. By comparing TAmiC with the classical centrality measures (which are solely based on the network structure) when simultaneously removing vertices, we show that this measure is correlated to degree and betweenness centrality measures, while its performance is generally better than that of closeness and eigenvector centrality measures. The results of this study suggest that TAmiC which represents a measure based on both network structure and biological knowledge, can successfully determine the important network components indicating that miRNA regulation and network robustness are related.

1. Introduction

1.1. Post-transcriptional regulation by microRNAs

MicroRNAs (miRNAs) are a growing class of small non-coding RNAs. These RNAs generally act as negative regulators of gene expression [1–3]. MiRNA-mRNA pairing, which leads to mRNA cleavage or translational repression, occurs in the seed (nucleotides 2–7) of miRNA. The "seed region" and degree to which a miRNA matches a potential mRNA target site has been extensively studied, and consequently, a number of miRNA target prediction methods have been introduced [4,5].

It has been previously shown that many miRNAs, act both on single target genes as well as systems level. For example, a number of genome-wide studies suggested that feedforward loops containing miRNAs are network motifs [6–8]. Following, we first discuss the basic concepts of network biology and its robustness, and then, review the current literature on the relationship between network structure and miRNA regulation.

1.2. Network biology

Complex biological systems can be represented by networks. In such a representation, each individual component is represented as a vertex (node) of the network. Additionally, each edge (link) that connects two vertices of the network, represents an interaction between two interacting components of the system [9,10]. Protein–protein interaction network (PPIN), metabolic network and signaling network are examples of active biological networks

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in a cell. Although biological networks are typically considered as static systems, in fact they are dynamic entities [11] influenced by gene regulation.

1.3. Network robustness

One of the key aspects of biological networks is the network robustness against the failure of its components [12,13]. Thus, an important question is to find out how perturbing the components of the system may affect the functionality of the network. It is clear that vertices of a given biological network are of different structural and functional importance. Therefore, detecting those vertices whose perturbation critically influences the structure and operation of a biological network is of great importance. The term "centrality measure" is referred to as a measure of "importance" of a vertex based on its connection to other network vertices [14]. The basic mathematical definitions used throughout this paper are introduced in details in Section 2.

Many classical studies on the robustness of networks have used the strategy of removing vertices at random, or alternatively, in descending order of vertex importance [15–18]. For example, in some of these studies, the vertices are firstly sorted based on their degree or betweenness centrality values. Then, the robustness of each network after removing important vertices has been investigated [19,20]. In a more recent comprehensive study [12], the importance of vertices of a wide variety of networks (including some empirical and model networks) was determined. Different measures of importance were investigated in this analysis, namely degree, betweenness, closeness and eigenvector centralities. Moreover, two strategies for removing important vertices, i.e., simultaneous vs. sequential targeted attack, were considered. It was shown that, generally, in case of simultaneous targeted attack, degree centrality was the best in detecting the most important vertices, while in sequential targeted attack betweenness centrality was the best measure. Furthermore, it was shown that robustness of a network may depend on different properties, such as degree distributions, clustering coefficient and coefficient of assortativity.

1.4. Biological networks and microRNA regulation

It has been proposed, based on network-based analyses, that miRNAs regulate biological networks through specific patterns. For example, using a reaction-centric model of human metabolic network, it has been shown [21] that miRNAs prefer to regulate hub nodes (the highly connected nodes) and cut points (the bottlenecks of metabolic flows), but not the intermediate nodes. In related works, several investigations were conducted to understand how miRNAs particularly regulate human's PPIN [11], signaling network [22], transcriptional regulation network [23] and cancer-related pathways [24]. In general, miRNAs appear to govern effectively the functional state of biological networks via controlling the essential elements of a network.

An accumulating body of efforts have been devoted to investigating potential effects of regulatory factors such as miRNAs on the robustness of functions in biological networks [25]. [26] suggested that *mir-7*, which operates on feedforward loops (FFLs) and feedback loops has a specific role in maintaining the network robustness against environmental perturbations. On the other hand, through a computational analysis, Osella et al. demonstrated that miRNAs accompanied by their target FFLs could buffer noise [27].

Therefore, the role of miRNAs in regulating some important network motifs (like FFLs) has been studied to some extent [26,27]. However, to the best of our knowledge, there is no comprehensive study on the relationship between miRNA regulation and the network-based importance of cellular components.

In the present study, we systematically analyzed the possible link between miRNA regulation and the robustness of biological networks. More precisely, we showed that miRNAs have a strong tendency for regulating those components that govern the network robustness. Based on these results, we introduce a "biology-based" measure to identify the potentially important vertices of a network. Finally, we compare this measure with the commonly used centrality measures, typically applied for identification of the important network components.

2. Materials and methods

2.1. Biological networks

In this study, the biological networks under investigation comprise three different versions of human protein–protein interaction networks, the human metabolic network, the human signaling network, and the *C. elegans* protein-protein interaction network.

- *PPINs*: The three PPINs used in this study are as follows. The first PPIN, namely CCSB-HI1, is a network containing 2754 edges obtained from a high-throughput yeast two-hybrid (Y2H) system. The second PPIN, that is LCI, includes 4067 literature curated protein–protein interactions. The third PPIN, which will be referred to as CCSB-HI1 + LCI, is basically constructed by merging the two above-mentioned PPINs. This network contains 6726 edges [28].
- *Signaling network*: The human signaling network is a literature-mined undirected network containing 540 nodes and 1257 edges, showing the signaling relationships between proteins [29].
- *Metabolic network*: We used a previously reported reaction-centric metabolic network of human [21], which is obtained from the KEGG database. This network includes 1099 vertices (i.e., reactions) and 4169 edges (i.e., linking metabolites).
- *PPIN of Caenorhabditis elegans* (*cPPIN*): This network contains 2500 nodes and 3706 edges established using a highly specific high-throughput Y2H system [30]. We included this network in our analysis to show that our findings are not limited to human networks, and similar patterns may be observed in other species.

2.2. Predicted miRNA targets

The genome-wide predicted human miRNA target genes were obtained from the TargetScanS web server (version 6.2) [31]. This dataset contains a total of 11,161 genes regulated by 6101 miRNAs (grouped in 153 conserved miRNA families). We also used another dataset of predicted miRNA target genes obtained from PicTar [32]. The latter dataset includes 6243 genes regulated by 168 miRNAs. The *C. elegans* miRNA target genes were acquired from the TargetScanS of worm (available at the http://www.targetscan.org/worm_52/).

2.3. List of essential genes

We obtained the human essential genes from the Database of Essential Genes (DEG) v10.6 [33] (available from: http://tubic.tju.edu.cn/deg). A list of 2570 human essential genes in this database are extracted from Liao et al. [34] and Georgi et al. [35].

2.4. List of oncogenes

A list of 780 candidate oncogenes used in this study are obtained from Khosravi et al. [36].