⮞ NETWORK BIOLOGY

Why do we need hubs?

Proteins that are hubs in interaction networks tend to be essential. Is this because deleting nodes that have multiple interactions reduces the overall connectivity of the network, or because hubs are more likely to be involved in an essential interaction? A new study of the yeast interaction network suggests that neither of these reasons provides the explanation. Instead, the authors provide evidence that essential proteins tend to belong to biological processes that are densely interconnected, and they are therefore more likely to be hubs.

With the increasing number of published interaction networks, it has been widely observed that hubs tend to correspond to essential genes. Although this seems intuitive, there has been disagreement about the underlying reason. The most popular explanation has been that hubs

mediate interactions between less connected proteins and therefore keep the network together. More recently, it has been suggested that it is single interactions that are important, and that because hubs are involved in more interactions they are more likely to be involved in one that is essential. Przytycka and colleagues set out to test these possibilities using published yeast interaction networks.

To limit the effect of artefacts the authors used six different variants of the *Saccharomyces cerevisiae* interaction network, from a combination of curated small-scale experiments and high-throughput data. They compared these with the results of a systematic yeast deletion screen that identified over 1,000 essential genes and confirmed the correlation between essentiality and hubs. They then showed that, in all the networks, removing essential hubs was no more disruptive than removing non-essential hubs. Furthermore, using a number of different network centrality measures, they demonstrated that the main topological determinant of essentiality is the node's local neighbourhood rather than global connectivity of the network.

To test the second model — that hubs are simply more likely to be involved in essential interactions owing to sheer force of numbers — the authors reasoned that, if that were the case, there should be no correlation between the chance of a

protein being essential and the chance of a near neighbour with which it does not interact being essential. This turned out not to be the case, leading the authors to propose their own alternative to the two previous models.

Based on their observations, the authors suggest that essential proteins tend to cluster in densely connected sub-networks with other proteins that are involved in the same biological process, and that these sub-networks are hub-rich. They refer to these clusters as essential complex biological modules. Using Gene Ontology to identify such clusters, they show that they are indeed enriched for essential hubs, whereas network hubs outside such modules are depleted in essential proteins.

These results demonstrate how a seemingly intuitive phenomena in networks can have a less intuitive explanation. They should also enable further explorations that look for connections between the properties of single interactions and those of the whole biological network, which more directly gives rise to the phenotype.

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