Assortativity signatures of transcription factor networks contribute to robustness

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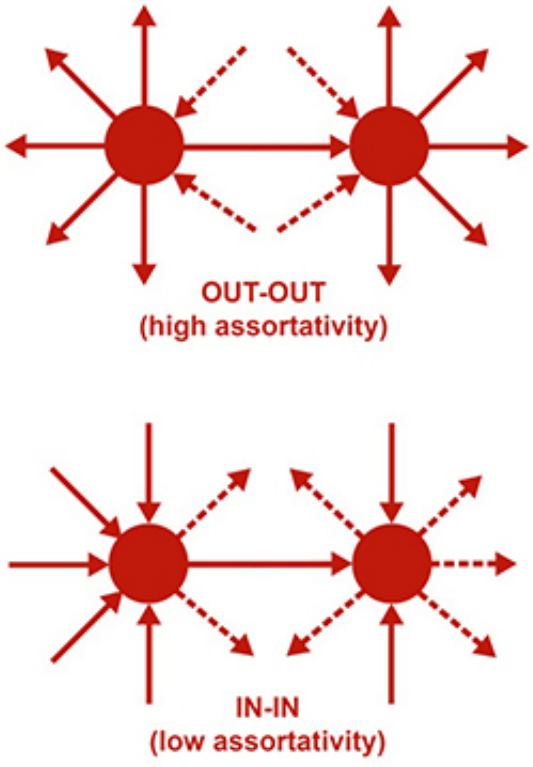

The assortativity of a TFN is calculated by looking at similarities and differences among pairs of TFs that are connected to one another. For example, connected TFs that have similar numbers of outgoing connections (top) will contribute to high out-out assortativity. Connected TFs that have differing numbers of incoming connections (bottom) will contribute to low in-in assortativity. By considering every pair of connected TFs across the entire TFN, the four types of assortativity (out-out, in-in, out-in, and in-out) can be computed.

Dartmouth researchers explored the type and number of connections in transcription factor networks (TFNs) to evaluate the role assortativity plays on robustness in a study published in *PLOS Computational Biology* in August. The study found that the assortativity signature contributes to a network's resilience against mutations.

"In simulations, it seems that varying the out-out assortativity of TFN models has a greater effect on robustness than varying any of the other three types of assortativity," said Dov A. Pechenick, PhD, lead author and former researcher at the Computational Genetics Laboratory at Dartmouth College, Hanover, NH. "We determined this by varying all four types of assortativity in the signature and then measuring robustness."

Transcription factors (TFs) are proteins that initiate and regulate the expression of a gene. To achieve their genetic mission, TFs also regulate one another's expression. Individual TFs connect to each other through connections that point in or out, forming a network. The direction of the coupling indicates regulatory control; an outbound connection by one TF stipulates its control over another, whereby it turns that TF on or off with respect to gene expression.

Many such connected pairings occur in a network, and their types determine a network's assortativity, which measures whether these pairings tend to occur between TFs that have similar numbers of connections. For example, when TFs in a pairing are likely to possess similar numbers of outgoing connections, out-out assortativity is high. If they are likely to possess very different numbers of incoming connections, in-in assortativity is low. Taken together, measures for the different kinds of assortativity create a signature. According to Pechenick, "There are four types of assortativity in directed networks, and the assortativity signature is a way of looking at all four at once."

Pechenick and his Dartmouth co-authors evaluated the assortativity signatures in published TFNs of 41 distinct human cell and tissue types and found that an above average number of connected TFs had similar numbers of outgoing connections (high out-out assortativity). Furthermore, this property, more so than the other three types of assortativity, seemed to be a predictor of robustness.

"Robustness is a measure of how resilient an overall pattern of TF gene expression is over time when confronted with mutations in the regulatory instructions of these TFs. If mutations tend to change the pattern, then robustness is low. If mutations tend to have no effect on the pattern, then robustness is high," said Pechenick.

This Dartmouth study was the first to look at the assortativity signatures of TFNs and their impact on robustness. "Results suggest that measuring the assortativity signature of a TFN can tell you something about its robustness," said Pechenick. "For researchers that wish to understand and simulate biological networks, these results indicate the importance of considering assortativity."

More information: *PLOS Computational Biology* , www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003780

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