BRIGHAM AND WOMEN'S HOSPITAL
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Channing Network Science Seminar

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Network-based prediction of protein interactions

As biological function emerges through interactions between a cell's molecular constituents, understanding cellular mechanisms requires us to catalogue all physical interactions between proteins. Despite spectacular advances in high-throughput mapping, the number of missing human protein-protein interactions (PPIs) continues to exceed the experimentally documented interactions. Computational tools that exploit structural, sequence or network topology information are increasingly used to fill in the gap, using the patterns of the already known interactome to predict undetected, yet biologically relevant interactions. Such network-based link prediction tools rely on the Triadic Closure Principle (TCP), stating that two proteins likely interact if they share multiple interaction partners. TCP is rooted in social network analysis, namely the observation that the more common friends two individuals have, the more likely that they know each other. Here, we offer direct empirical evidence across multiple organisms that, despite its dominant use in biological link prediction, TCP is not valid for most protein pairs. We show that this failure is fundamental - TCP violates both structural constraints and evolutionary processes. This understanding allows us to propose a link prediction principle, consistent with both structural and evolutionary arguments, that predicts yet uncovered protein interactions based on paths of length three (L3). A systematic computational cross-validation shows that the L3 principle significantly outperforms existing link prediction methods. To experimentally test the L3 predictions, we perform both large-scale high-throughput and pair-wise tests, finding that the predicted links test positively at the same rate as previously known interactions, suggesting that most (if not all) predicted interactions are real. Combining L3 predictions with experimental tests provided new interaction partners of FAM161A, a protein linked to retinitis pigmentosa, offering novel insights into the molecular mechanisms that lead to the disease. We expect L3 to have a broad applicability, enabling us to better understand the emergence of biological function under both healthy and pathological conditions.

BIO: István Kovács, Ph.D., is working on bridging the gap between structure and function in complex systems, in the group of Prof. Barabási at Northeastern University. He is developing novel methodologies to predict the emerging structural and functional patterns in a broad spectrum of problems ranging from systems biology to quantum physics, in close collaboration with experimental groups.

Hosted by Yang-Yu Liu