

# NETWORK BIOLOGY—AT THE FRONTIER



**L**iving systems are characterized by intricate networks of interactions among tens of thousands of entities within cells and across extracellular milieus. The entities in these networks include such things as genes, proteins, and small molecules. The interactions describe relationships such as transcriptional regulation, posttranslational modification, and complex formation, among others.

Our understanding of phenomena like disease states, responses to toxins, and basic biological processes such as circadian rhythms and cellular differentiation, hinges on our ability to characterize and make inferences about these networks. This challenge is daunting given that the processes defined by the networks are dynamic; the relevant entities and interactions in the networks vary across cell types and contexts; and our knowledge of the entities and interactions is incomplete even for the simplest, single-cell organisms. Nevertheless, substantial progress is being made in developing computational methods that augment our understanding of the biological networks underlying processes, responses and states of interest. As highlighted in this issue, computational network biology is rapidly advancing with innovations on several important fronts.

*Addressing incompleteness.* The gaps in our knowledge of intracellular networks are being partially filled in by novel technologies for more thoroughly identifying specific types of interactions such as the protein-protein interactions that are being detected in the BioPlex project at Harvard. An alternative strategy to handling incompleteness is to screen for genetic interactions using knockout or knockdown methods. Novel algorithms are being developed to make inferences about how sets of gene products interact based on the results of these genetic-interaction screens.

*Incorporating multiple types of interactions.* Although useful inferences can sometimes be made by analyzing networks composed from a single type of interaction (e.g. protein-protein interaction or gene co-expression), we can clearly gain higher fidelity representations of biological processes by constructing and reasoning with network models that incorporate multiple types of interactions.

*Network descriptions of diseases and patients.* Whereas early network models focused on routine processes in model organisms, recent research has demonstrated that network

models can provide insight into diseases as varied as autism, breast cancer, Parkinson's (described in this issue), and viral infections.<sup>1</sup> Moreover, many of the algorithms that have been applied to intracellular networks can be applied to other types of networks, such as patient similarity networks in which the nodes represent patients and the edges represent phenotypic similarity.

*Exploiting relationships among organisms and cell types.* Gaps in our understanding of networks in one type of cell can often be alleviated by taking advantage of information from related cells.<sup>2</sup> For example, the TransposeNet method described in this issue has aided in the characterization of relationships among Parkinson's risk genes by mapping a relevant subnetwork from yeast onto an inferred human network.

In addition to these avenues of research, there are other directions where we can expect to see significant innovations in the near future. One important challenge is to devise network models that provide more expressive and faithful representations of the underlying biology. Such models will incorporate representations of epigenetics, cellular compartments, spatial and transport relationships, intercellular interactions, and host-microbiome interactions, among other aspects. A second area that is ripe for further exploration entails approaches that specify how network responses change as a function of genetic variation and environmental exposures. Another promising area: algorithms for optimally selecting the most informative experiments to refine network models.<sup>3</sup> And a fourth key direction is devising network models that span multiple scales, from molecules to whole organisms and their microbiomes. Such network models hold the promise of capturing in substantial detail how patient-level descriptors like symptoms and diseases are manifested all the way down to the molecular level, thus helping to drive advances in precision medicine. □

## References

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