RECONSTRUCTING THE CIRCUITS OF DISEASE: FROM MOLECULAR STATES TO PHYSIOLOGICAL STATES

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Abstract
Common human diseases and drug response are complex traits that involve entire networks of changes at the molecular level driven by genetic and environmental perturbations. Efforts to elucidate disease and drug response traits have focused on single dimensions of the system. Studies focused on identifying changes in DNA that correlate with changes in disease or drug response traits, changes in gene expression that correlate with disease or drug response traits, or changes in other molecular traits (e.g., metabolite, methylation status, protein phosphorylation status, and so on) that correlate with disease or drug response are fairly routine and have met with great success in many cases. However, to further our understanding of the complex network of molecular and cellular changes that impact disease risk, disease progression, severity, and drug response, these multiple dimensions must be considered together. Here I present an approach for integrating a diversity of molecular and clinical trait data to uncover models that predict complex system behavior. By integrating diverse types of data on a large scale I demonstrate that some forms of common human diseases are most likely the result of perturbations to specific gene networks that in turn causes changes in the states of other gene networks both within and between tissues that drive biological processes associated with disease. These models elucidate not only primary drivers of disease and drug response, but they provide a context within which to interpret biological function, beyond what could be achieved by looking at one dimension alone. That some forms of common human diseases are the result of complex interactions among networks has significant implications for drug discovery: designing drugs or drug combinations to impact entire network states rather than designing drugs that target specific disease associated genes.