Functional interpretation of genomes using biological networks

The recent explosion in genome-wide association studies and exome sequencing projects have revealed many genetic variants likely to be involved in disease processes, but the composition and function of the tissue-specific molecular systems they affect remain largely obscure. This limits our progress towards biological understanding and therapeutic intervention. Computational analyses that systematically integrate biological networks (i.e., networks in which genes are connected if they are functionally associated in some experimental system) with genetic data have emerged as a powerful and scalable approach to functionally interpret very large genomic data sets by enabling the identification of *de novo* pathways perturbed in disease. This talk will highlight approaches and methods we have developed in this area, and exemplify how different network-based methods have been used to analyze common and rare genetic variants to deduce the molecular networks perturbed by genetics in a wide range of diseases. As a general model for how *in silico* networks can be expanded, consolidated and validated, I will show how protein-protein interaction networks involved in human arrhythmias were elucidated and validated by combining, GWAS, quantitative interaction proteomics, electrophysiology and model organisms through rigorous statistical frameworks. I will also illustrate how we are now applying this approach to cancers as well as neuropsychiatric and cardiovascular diseases.