

Using Network Flow to Bridge the Gap between Genotype and Phenotype

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It is now being recognized that complex diseases should be studied from the perspective of dys-regulated pathways and processes rather than individual genes. Indeed, various combinations of molecular perturbations often lead to the same disease suggesting that, on a molecular level, they dys-regulate the same cellular pathways. In addition, signals that are associated with each individual perturbation might be weak, rendering studies of complex diseases particularly challenging.

Based in the assumption that that disease-associated gene expression changes are by and large caused by genomic alterations, we can begin to determine potential paths from such genomic causes to target genes. We utilized graph-theoretical techniques and combinatorial algorithms to determine potential paths from the genomic causes through a network of molecular interactions. Such approach allows for uncovering candidate causal genes and causal paths that are potentially responsible for the altered expression of disease genes. Particularly interesting are overlaps between such pathways as they indicated commonly dys-regulated pathway and disease “hubs”.

I will discuss application of a graph-theoretical network flow approach to sets of genomic alterations and gene expression profiles of Glioblastoma multiforme (GBM) patients. This approach pointed to candidate causal genes and causal paths that are potentially responsible for the altered expression of disease associated target genes.