Emergence and propagation of epistasis in metabolic networks

Abstract:

Epistasis is a situation when the effect of one mutation changes as other mutations are introduced into the genome. Epistasis is used in genetics to probe functional relationships between genes, and it also plays an important role in evolution. However, there is no theory to understand how functional relationships at the molecular level translate into epistasis at the level of whole-organism phenotypes, such as fitness. I will present a simple model of a hierarchical metabolic network with first-order kinetics which helps us gain some intuition in this problem. I will derive two rules for how epistasis between mutations with small effects propagates from lower- to higher-level phenotypes and how such epistasis depends on the topology of the network. Most importantly, weak epistasis at a lower level may be distorted as it propagates to higher levels. These results suggest that pairwise inter-gene epistasis should be common and it should generically depend on the genetic background and environment. Furthermore, the epistasis coefficients measured for high-level phenotypes may not be sufficient to fully infer the underlying functional relationships.