304c Graph Theory-Flux Analysis Framework for Tissue-Specific Modeling of Metabolic Network Structure and Function

Ryan P. Nolan, Yaguang Si, and Kyongbum Lee

Directed manipulation of cellular metabolism requires an appropriate blueprint of the system. Cellular metabolism consist of hundreds of highly interconnected metabolites and reactions, which presents significant challenges to modeling. Annotated genome databases, which often form the basis for reaction network models, refer to entire organisms. In the case of higher animals with specialized tissues, these models lack physiological relevance, because a given tissue expresses only a fraction of the metabolic genes of the organism.

In this work, we present a framework for relating the structural and functional elements of cellular metabolism, which should be particularly useful for studying cells of higher organisms relevant to biomedical investigations. We first reduce a genomic-scale metabolic reaction network to tissue (or cell type)-specific subnetworks, which are then characterized in greater detail. Graph theory is used to determine structural or enzyme-mediated connectivity relationships between metabolites and reactions. Finally, we scale the network graphs with metabolic flux data, and thereby incorporate information on functional reaction coordination reflecting metabolic activity correlation between reactions. To calculate fluxes, we develop an optimization-based algorithm that uses measured external fluxes, stoichiometry, and pathway Gibbs free energies as constraints.

We applied the above framework to the liver and adipose tissue. Reaction network models were generated independently for each tissue. Graph analysis revealed different structural connectivity relationships for each tissue; these differences were further underscored by incorporation of flux data. The liver showed a high degree of coupling between the urea cycle, TCA cycle, aspartate cycle, glycolysis, and the PPP. The adipose tissue showed a high degree of coupling between the TCA cycle, malate cycle, glycolysis, and fatty acid synthesis. Our findings point to significant conservation of both structural and functional connectivity between the three central carbon metabolism pathways.