Contribution of Network Connectivity in Determining the Relationship between Gene Expression and Metabolite Concentration Changes

One of the primary mechanisms through which a cell exerts control over its metabolic state is by modulating expression levels of its enzyme-coding genes. However, the changes at the level of enzyme expression allow only indirect control over metabolite levels, for two main reasons. First, at the level of individual reactions, metabolite levels are non-linearly dependent on enzyme abundances as per the reaction kinetics mechanisms. Secondly, specific metabolite pools are tightly interlinked with the rest of the metabolic network through their production and consumption reactions. While the role of reaction kinetics in metabolite concentration control is well studied at the level of individual reactions, the contribution of network connectivity has remained relatively unclear. Here we report a modeling framework that integrates both reaction kinetics and network connectivity constraints for describing the interplay between metabolite concentrations and mRNA levels. We used this framework to investigate correlations between the gene expression and the metabolite concentration changes in Saccharomyces cerevisiae during its metabolic cycle, as well as in response to three fundamentally different biological perturbations, namely gene knockout, nutrient shock and nutrient change. While the kinetic constraints applied at the level of individual reactions were found to be poor descriptors of the mRNA-metabolite relationship, their use in the context of the network enabled us to correlate changes in the expression of enzyme-coding genes to the alterations in metabolite levels. Our results highlight the key contribution of metabolic network connectivity in mediating cellular control over metabolite levels, and have implications towards bridging the gap between genotype and metabolic phenotype.

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