Modeling the Contribution of Allosteric Regulation for Flux Control in the Central Carbon Metabolism of E. coli - DTU Orbit (24/12/2018)

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Modeling cellular metabolism is fundamental for many biotechnological applications, including drug discovery and rational cell factory design. Central carbon metabolism (CCM) is particularly important as it provides the energy and precursors for other biological processes. However, the complex regulation of CCM pathways has still not been fully unraveled and recent studies have shown that CCM is mostly regulated at post-transcriptional levels. In order to better understand the role of allosteric regulation in controlling the metabolic phenotype, we expand the reconstruction of CCM in Escherichia coli with allosteric interactions obtained from relevant databases. This model is used to integrate multi-omics datasets and analyze the coordinated changes in enzyme, metabolite, and flux levels between multiple experimental conditions. We observe cases where allosteric interactions have a major contribution to the metabolic flux changes. Inspired by these results, we develop a constraint-based method (arFBA) for simulation of metabolic flux distributions that accounts for allosteric interactions. This method can be used for systematic prediction of potential allosteric regulation under the given experimental conditions based on experimental data. We show that arFBA allows predicting coordinated flux changes that would not be predicted without considering allosteric regulation. The results reveal the importance of key regulatory metabolites, such as fructose-1,6-bisphosphate, in controlling the metabolic flux. Accounting for allosteric interactions in metabolic reconstructions reveals a hidden topology in metabolic networks, improving our understanding of cellular metabolism and fostering the development of novel simulation methods that account for this type of regulation.

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