Dynamic optimization of metabolic networks coupled with gene expression

Adjusting the metabolic network organization to the environment by tuning enzyme expression levels is crucial for cellular growth, in particular in a changing environment or during metabolic adaptation. Metabolic networks are often studied with optimization methods applied to constraint-based steady-state models. But, a corresponding dynamic modeling framework including a tight interplay between metabolic fluxes and gene expression is currently lacking. Due to that, the cost of producing enzymes so far could not be taken into account in dynamic optimization of metabolic fluxes. Here, we present a modeling framework combining the metabolic network and the enzyme production costs. Model reduction using timescale separation yields a coupled model of quasi steady-state constraints on the metabolic reactions, and differential equations for the substrate concentrations and biomass composition. Based on this model, we propose a dynamic optimization approach to determine reaction fluxes, explicitly taking production costs for enzymes and enzymatic capacity into account. In contrast to the established dynamic flux balance analysis, the proposed approach thereby allows to analyse dynamic changes in both the metabolic fluxes and the detailed biomass composition in situations of metabolic adaptation.

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