

533d An Optimization Framework for Identifying Reaction Activation/Inhibition or Elimination Candidates for Overproduction in Microbial Systems

Priti Pharkya and Costas D. Maranas

Computational models serve as important tools in strain design by enabling systemic analysis of genetic manipulations introduced into the metabolic network of an organism. In this talk, we will introduce an optimization framework termed OptReg that determines the optimal reaction activations/inhibitions and eliminations for targeted biochemical production. A reaction is deemed up or down regulated if it is constrained to assume flux significantly above or below its respective steady-state values. The extent of deviation of a flux from its steady state values is quantified by using the “regulation strength parameter”. Steady state fluxes for some of the reactions in central metabolism of *Escherichia coli* are fixed at experimental values available in literature. The remaining fluxes are estimated computationally using a series of linear programming problems. The computational difficulties arising due to hundreds of binary variables and bilinear products of binary and continuous variables make this a challenging problem to solve.

The developed framework is demonstrated by studying the overproduction of ethanol in *Escherichia coli*. Computational results reveal the existence of synergism between reaction deletions and modulations implying that the simultaneous application of both types of genetic manipulations yields the most promising results. For example, the downregulation of *phosphoglucomutase* in conjunction with the deletion of oxygen uptake and *pyruvate formate lyase* yields 99.8% of the maximum theoretical ethanol yield. Conceptually, the proposed strategies redirect both the carbon flux as well as the cofactors to enhance ethanol production in the network. In many cases, the predictions made by the framework pinpoint the crucial role played by cofactor availability in biochemical overproduction. The OptReg framework is therefore a versatile tool for strain design which allows for a broad array of genetic manipulations.