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Towards bioprocess control based on a reduced metabolic model of *Escherichia coli*

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Abstract

Most mathematical models used for optimization and control of biotechnological processes are relatively simple and the complex interactions between the extracellular environment and the thousands of intracellular enzymes and metabolites are generally ignored. The lack of this information in bioreactor monitoring and control can have a profound impact on biological systems. Nevertheless, the use of model-based methods in process monitoring and control is nowadays limited due to their complexity and the lack of appropriate methodologies. The challenge of the development of a model that predicts the dynamic response of cellular phenotypes to environmental conditions is not yet solved and will be addressed in the view of bioprocess control. First, stoichiometric models represent an infinite number of possible phenotypes; systems biology tools need to be applied such that the simulation matches the phenotypes in given conditions. Second, most tools in systems biology are designed for steady-state applications, whereas the aim of process control requires a dynamic approach. Third, as a consequence of the complexity of the models, the computational intensity is high.

One tool that has the potential to solve the above problems is Elementary Modes. EMs analysis identifies all minimal functional pathways possibilities inherent to a metabolic network. A consideration in the analysis of EMs for large metabolic networks is the problem of combinatorial explosion of possible routes across the networks. In many situations, more EMs exist than necessary to construct all admissible flux distributions. Therefore, some of them can be taken as a generator set of the whole admissible region. In this work, a controlled random search (CRS) algorithm combined with nonnegative least squares is developed to select a limited number of EMs matching the observed phenotype. The method minimizes the objective function in an iterative search. The objective function to be minimized consists of the weighted sum of squared errors and a penalty for inefficiency of each EM and for model size.

This case study considered the central carbon metabolism of *E. coli*. A single EM or a linear combination of EMs could be selected to match the experimental data. Using the CRS algorithm, the original model with 2706 EMs was reduced to a system of 3 modes for biomass growth, acetate production, and maintenance purposes that gives a good correlation with the measured data.