MODEL-BASED MEDIUM OPTIMIZATION METHODOLOGIES IN HIGH-CELL DENSITY PERFUSION CULTURE

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Key Words: Perfusion cultures, Medium optimization, Model-based techniques

The goal of the present study is to develop and assess model-based techniques for medium optimization in high-cell density perfusion cultures. The approach takes advantage of a mechanistic kinetic metabolic model to design media that can optimize productivity and harvested amount of a product of interest - while taking into account solubility issues and desirable bounds on toxic byproducts - without the need of an extensive search in the design space, thus reducing the number of experiments needed for process development.

The study was performed with CHO-K1 cells producing a monoclonal antibody (mAb). The model-based optimization used a mechanistic kinetic model of the central cell metabolism, defined by a reaction network of 126 reactions, using elementary flux modes determined by column generation [1] and kinetic parameters estimated by Bayesian estimation techniques. A first approach formulates an optimization problem, with the objective function reflecting the amount of harvested mAb. Bounds on the amount of ammonium and lactate produced, as well as constraints on the possible perfusion medium composition, are enforced through the optimization procedure. The sensitivity of the obtained solution is then checked, by considering different perturbed realizations of the optimized solution, and simulating the model response for these perturbations. In such optimization problems many local minima naturally occur, meaning that different runs of optimization are executed starting from different initial conditions. After new experimental conditions are decided, the results from the new experiment are used to update the metabolic network model, which inherently contains uncertainty, making this approach iterative in nature.

In the second approach, uncertainties are explicitly accounted for, both in terms of parametric uncertainties in the mathematical model, as well as possible unavoidable medium preparation errors [2]. The optimization is performed by maximizing the worst-case yield over all models that can explain the data reasonably well. Inspired from Reinforcement Learning and Bayesian Optimization, the method successively explores different compositions experimentally. Through optimal experiment design and model update, we repeatedly reduce uncertainties in the region where the likelihood of improvement on the worst-case mAb productivity is maximized. This means that the overall experimental effort can be reduced as compared to a priori determining which compositions to be used, as in classical design of experiments techniques. By applying the proposed approach, a robust medium composition with productivity guarantees under various uncertainties is obtained.

References:
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