In-silico media optimization for continuous cultures using genome scale metabolic networks: the case of CHO-K1

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Abstract

The cell culture is the central piece of a biotechnological industrial process. It includes upstream (e.g. media preparation, fixed costs, etc.) and downstream steps (e.g. product purification, waste disposal, etc.). In the continuous mode of cell culture, a constant flow of fresh media replaces culture fluid until the system reaches a steady state. This steady state is the standard operation mode which, under very general conditions, is a function of the ratio between the cell density and the dilution rate and depends on the media supplied to the culture. To optimize the production process it is widely accepted that the concentration of the metabolites in this media should be careful tuned. A poor media may not provide enough nutrients to the culture, while a media too rich in nutrients may be a waste of resources because, either the cells do not use all of the available nutrients, or worse, they over-consume them producing toxic byproducts. In this work we show how an in-silico study of a genome scale metabolic network coupled to the dynamics of a chemostat could guide the strategy to optimize the media to be used in a continuous process. Given a known media we model the concentrations of the cells in a chemostat as a function of the dilution rate. Then, we cast the problem of optimizing the production process within a linear programming framework in which the goal is to minimize the cost of the media keeping fixed the cell concentration for a given dilution rate in the chemostat. We evaluate our results in two metabolic models: first a simplified model of mammalian cell metabolism, and then in a realistic genome-scale metabolic networks of mammalian cells, the Chinese Hamster Ovary (CHO) cell line. We explore the latter in more detail given specific meaning to the predictions of the concentrations of several metabolites.

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