A PRIORI OPTIMIZATION OF CELL CULTURE FEEDS USING METABOLIC ENGINEERING

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Traditional media optimization procedures, such as component titration and spent media analysis, are costly, time consuming and frequently rely on heuristics that differ between scientists to reduce the amount of chemical species, and their respective concentration ranges, to investigate – which can result in suboptimal media compositions for promoting cell growth. This is despite the fact that cellular metabolism provides a mechanistic framework for assessing the impact of media composition, and by extension feed composition, on cell growth. The highly nonlinear relationship between media component concentration and cell growth, or biomass production, has precluded the use of standard regression techniques to optimize the cell culture feeds over a wide range of conditions – but metabolic engineering techniques are a promising alternative. Currently, the population's metabolic state can be well described, in aggregate, with metabolic flux analysis techniques; it has already been shown that flux balance analysis (FBA) is a useful tool for the a posteriori phenotyping of a cell culture in academic settings. However, a frequent criticism of FBA is that there is not a practical way for manufacturers to realize the purported benefits of this technique. In this work, the amino acid transport fluxes were measured during the exponential growth phase of a CHO cell culture and used as constraints for a FBA model. This served as the center point of an in Silico design of experiment (DoE) that was performed by perturbing the measured fluxes and generating a new FBA model with the perturbed fluxes used as model constraints. The DoE results allow for an assessment of the impact that amino acid supplementation will have on the ongoing cell culture a priori. The results show that feeding tyrosine, cysteine, proline and asparagine increased the duration of the exponential growth phase by 70% in normal batches. In addition, the growth rate was doubled for a batch in which growth was stunted after its pH control failed due to a faulty sensor. Overall, this work demonstrates a practical application of FBA that will improve yields and reduce losses while significantly reducing the time and economic requirements necessary for extensive experimentation. Caveats and expected future improvements are also explored. Disclaimer: This article reflects the views of the authors and should not be construed to represent official FDA's views or policies.