AMINO ACID ANALYSIS TO SUPPORT A GENOME-SCALE NUTRIENT MINIMIZATION FORECAST ALGORITHM FOR CONTROLLING ESSENTIAL AMINO ACID LEVELS IN CHO CELL CULTURES

Ji Young L. Anderson, 908 Devices Inc., Boston, MA, USA
janderson@908devices.com
Yiqun Chen, John Hopkins University,
Harnish Mukesh Naik, John Hopkins University,
Venkata Gayatri Dhara, John Hopkins University,
Michael J. Betenbaugh, John Hopkins University

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Process control of mammalian cell cultures is inhibited due to the limited understanding of cell metabolism and the inability to predict cell behaviors. This study describes the development and testing of a forecast-based feeding approach to control Chinese hamster ovary (CHO) processes. The model uses easily acquired viable cell density data to predict multiple essential amino acid levels in the culture. The cell growth behavior forecast was first tested for fit with prior batch growth datasets for CHO cells. The growth forecast model was combined with the nutrient-minimized CHO genome-scale model to generate essential amino acid forecast profiles. To build and test the model, cell viability, viable cell density, amino acid concentrations, glucose, lactate, and titer measurements were acquired via spent media analysis. Daily amino acid measurements were accomplished using the REBEL, an automated at-line capillary electrophoresis (CE) mass spectrometry (MS) device that quantitates amino acid concentrations in under 10 minutes per sample. The forecast algorithm was found to accurately predict the concentrations of most essential amino acids from cell density measurements with error mitigated by incorporating amino acid concentration measurements.

Here, we present the design of a proof-of-concept algorithm-guided amino acid feeding control experiment and the results from fed-batch CHO cell cultures. CHO cultures were divided into two different groups, an empirical and forecast-guided fed-batch culture. The forecast-guided approach was designed to control the concentration of leucine, lysine, and valine below 1-2 mM over a 9-day culture. The forecast-guided culture maintained comparable growth behavior to the empirical-based culture. Due to metabolic shifts in branch-chain amino acid degradation, the forecast-guided cultures also displayed elevated glycine production, reduced alanine concentrations, and slightly lower lactate production.

The algorithm developed aims to inform a dynamic process model with minimal measurement inputs during the final bioprocess. Using daily cell viability measurements and amino acid concentrations, the model can provide valuable foresight into CHO and other mammalian cell-based systems. This cost-effective and informative tool provides researchers the ability to design better process control strategies such as feeding schemes or media composition leading to enhanced control over CHO and other mammalian cell-based bioprocesses.

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