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Fluxomics: The integration of metabolic flux analysis (MFA) with multivariate data analysis (MVDA) to identify key process parameters for CHO cell culture

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Abstract:

An integrated ^{13}C-metabolic flux analysis (MFA)/fluxomics approach was conducted to characterize fed-batch, concentrated fed-batch, and perfusion modes of operation. While both the concentrated fed-batch and perfusion processes were independently represented by one metabolic quasi-steady-state, fed-batch metabolism was characterized by multiple. Intracellular flux maps were developed for all three operational modes. To elucidate the phenotype of peak specific productivity, the stationary phase of fed-batch was characterized by ^{13}C-MFA. The metabolic network included glycolysis, the pentose-phosphate pathway, citric acid cycle, and various anaplerotic reactions. Anabolic demands for biomass, host cell protein (HCP), and IgG were accounted for. To identify potential rate limitations and catabolic metabolite contributions, a stoichiometric model was created, considering the aforementioned anabolic demands relative to the observed specific consumption rates.

Additionally, to foster a more holistic understanding of fed-batch, specific consumption/production rates were determined for all phases of fed-batch, from inoculation to harvest. Multiple feeding strategies, inoculation densities, and CHO cell lines were evaluated for the fed-batch process. Incorporating the intracellular flux networks from all three operational modes, multivariate data analysis (MVDA) was then employed to statistically determine the correlation of metabolic fluxes with final titer/specific productivity. For fed-batch, fluxes with temporal resolution were included. Interestingly, some of the best predictors of final titer (top 5% among all variables) were fluxes measured in the first two days of culture. One such example was specific productivity, a variable generally not considered at such an early stage. Conversely, specific lactate production over the first two days of culture, while typically at its maximum, hardly correlated (positively or negatively) with final titer at all. We will discuss the impact of using fluxomics, made possible through the integration of MVDA with MFA, to assess and identify key process parameters for antibody production.