Debottlenecking and reformulating feed media for improved CHO cell growth and titer by data-driven and model-guided analyses

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Abstract

Designing and selecting cell culture media and their feeding are a key strategy to maximize culture performance in industrial biopharmaceutical processes. However, mammalian cells are very sensitive to their culture environment, requiring specific nutritional needs to grow and produce high-quality proteins such as antibodies, depending on cell lines and operational conditions. In this regard, previously we developed data-driven and in-silico model-guided systematic framework to investigate the effect of growth media on Chinese hamster ovary (CHO) cell culture performance, allowing us to design and reformulate basal media. To expand our exploration for media development research further, we evaluated two chemically defined feed media, A and B, in ambr15 bioreactor runs using a monoclonal antibody-producing CHO K1 cell line. We observed a significant impact of feed media on cell growth, longevity, viability, productivity and toxic metabolites production. Specifically, concentrated feed A was not sufficient to support prolonged cell culture and high titer compared to feed B. The framework systematically characterized the major metabolic bottlenecks in the TCA cycle and its related amino acid transferase reactions, thereby identifying key design components, such as asparagine, aspartate, and glutamate, which are needed for highly productive cell cultures. Based on our results, we subsequently reformulated the feeds by adjusting the amounts of those amino acids and successfully validated their effectiveness in promoting cell growth and/or titer.

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