A LESS-TRAVELED PATH FOR DATA IN BIOPROCESS DEVELOPMENT: FROM DYNAMIC EXPERIMENTS TO DYNAMIC PROCESS MODELS

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Therapeutic monoclonal antibodies (mAbs) are typically manufactured in a tightly controlled fed-batch bioreactor environment. Process conditions and the feeding strategy for nutrient supplementation critically affect the growth and metabolic behaviors of cells, which in turn determine the final product titer and quality. In bioprocess development, we rely largely on a trial-and-error procedure based on sparsely designed experiments. Design of experiments (DoE) addresses this issue by allowing us to analyze the effect of process inputs on process responses systematically and efficiently; however, DoE cannot be applied directly to study time-varying process inputs unless an impractically large number of reactors is used. Here, we present the results from a design of dynamic experiments (DoDE) to model the effect of dynamic feeding on the performance of a mAb manufacturing process without violating our reactor limit. Our effort resulted in tangible and reproducible improvement in productivity—a 27% increase in product titer of a proprietary mAb manufacturing process without affecting product quality attributes significantly.

While a statistical model based on the DoDE data was proved useful in optimizing a dynamic feed, one can only use the model to predict end-of-run quantities but not the trajectories leading to them. We exploited the rich time-series DoDE data further by developing a dynamic process model that captures how different process variables change over time. The linear state-space model has eight state variables and two input variables. The model parameters were estimated using time-series data from 15 DoDE batches, and the model was tested against a testing dataset of two batches from the same DoDE. We optimized the feeding strategy of a fed-batch process *in silico* based on the model. We anticipate such a dynamic process model to be a crucial part of an advanced, model-based process control system that integrates model predictive control and state estimation to control productivity and product quality attributes by changing feed rates and other process conditions adaptively. We also recognize the unique promises and challenges of creating such an advanced process control system in bioprocess development.