Enhancing Automated Sampling, Process Monitoring, and Nutrient Feedback Control for a System of 3 L Bioreactors

Kristin O’Neill; Linda Hoshan; T. Craig Seamsans
BioProcess Development, Merck & Co., Inc., Kenilworth, NJ, USA
kristin.oneill@merck.com

Abstract
Background and Novelty
Key to effective upstream development is the presence of resource-efficient systems for examining complex process options. In this presentation we report on the progress of a completely automated sampling and feed control system capable of simultaneously evaluating different metabolic-based feed strategies for bench-scale cell culture processes. Through this research, we are learning to control multiple culture vessels, to date there is not a complete 3 L scale sample and feed automation solution as described here, capable to transfer samples from multiple bioreactors (single-use or pass) to a suite of independent analyzers and constant feedback control of nutrient feed pumps. There are multiple drivers for developing automated systems for benchtop bioreactors, ranging from increased operational efficiency to enhancing the toolbox for process development. Deeper process understanding, obtained through simultaneous metabolic sensing, is essential to the development of state-of-the-art upstream processes with emphasis on product quality attributes.

Experimental Approach
The automated online sampling and feed system is capable of feedback control for a variety of complex feed strategies that incorporate data inputs from integrated third-party analyzers. Feed control inputs can be cell density and/or up to four measured residual metabolites. The completely automated system has supported experiments from two to eight 3 L bioreactors, with sampling frequencies ranging from 4 to 24 hours per tank, depending upon experimental needs.

Results and Discussion
In a recent typical experiment, eight tanks were sampled three times per day with feedback control for multiple separate nutrient feed solutions per tank, based upon independent metabolic triggers. Over the course of the run, each vessel was triggered feeds 35 to 40 times with feed volumes ranging from 2 to 40 mL for over ~350 automated feeds across the eight vessels. Refined data extraction templates streamlined data inputs into the electronic notebook system, and PI integration can enable remote monitoring. The enhanced system capabilities are being increasingly leveraged to support ongoing process development efforts.

IMPACT OF SYSTEM LAYOUT ON CYCLE TIME AND SAMPLE DELIVERY

SUCCESSFUL ONLINE PROCESS MONITORING

REMOTE MONITORING ENABLED BY INTEGRATION OF SEG-FLOW WITH PI HISTORIAN

SUMMARY

Innovative effort led to sophisticated bench-scale automation
- Real-time bioreactors
- Cell-free containing samples
- Three instrument analyzers
- Four automated feeds per reactor
- Custom software data for easy export/import
- Remote monitoring enabled by PI integration

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