A HIGHLY AUTOMATED, CONTINUOUS METHOD FOR DEVELOPING ACTIVE CONTROLLERS OF PRODUCT QUALITY ATTRIBUTES IN EARLY PHASE CLINICAL DEVELOPMENT

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The biotherapeutics industry is aggressively targeting increases in product quality. It has been recently suggested that a 10x increase in robustness of product quality will be required in the next 5-10 years to meet the changing market forces of our industry[1]. This step-increase in quality will likely only be achieved by actively controlling product quality attributes in bioproduction processes, using techniques like model predictive control (MPC)[2]. Adoption of MPC of product quality attributes in bioproduction processes has been somewhat sluggish, despite the recent introduction of enabling technologies, such as aseptic auto samplers. One barrier for adoption of MPC is the current difficulty involved in developing MPC controllers. This difficulty stems from the fact that critical to quality process technologies like MPC must be adopted early in the drug development process to achieve consistent clinical material throughout the drug development process. There remains a need for a method to quickly and cheaply develop MPC strategies during early phase development for biomanufacturing processes.

To address this barrier to early phase adoption of MPC, we developed a novel MPC development method which we believe is fast, inexpensive, and robust enough to be applied in early-stage bioreactor development programs. The proposed method measures the dynamic behavior of product quality attributes in response to modulations in media component concentrations. The method is enabled by a system which performs a series of automated, short (1-4 days), continuous experiments by using an automated perfusion apparatus to perform step-change experiments on the actual clone/media system proposed for the clinical bioreactor process. The resulting responses in product quality attributes are captured using automated analytical technologies, and the resulting dynamic quality data is used to create a model predictive controller in a systematic fashion. The result is a system which is capable of systematically generating model predictive controllers based on identified critical process parameters and the impacted critical quality attributes (CQAs). Here we show a proof of concept study, where all major components of the above described method were used to develop a model predictive controller for galactosylation of a monoclonal antibody, using galactose feed as the control handle. Experimental validation of the model used in the model predictive controller was demonstrated using a set of external fed-batch validation runs. We then demonstrated the controller's ability to achieve a set galactosylation value in a simulated fed-batch process with variable galactose feeding (Figure 1).

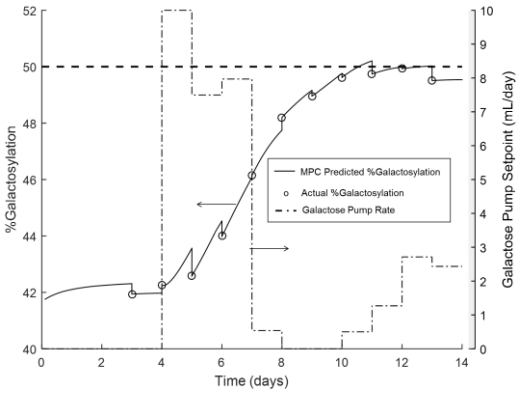

Figure 1 – *Control chart of %galactosylation controlled by MPC-based feeding of galactose in a fed-batch process.*

Using the method demonstrated here, we suggest that variation in product quality attributes can be actively controlled with much less process development effort than is typically used (e.g., batch DOE methodologies). This decrease in effort is achieved through heavy application of automation and short, continuous bioreactor studies. The ability to actively control product quality attributes using model predictive control and system identification strategies may catalyze wider adoption of active control of product quality attributes earlier in the development cycle, and we hope will accelerate adoption of MPC to achieve tighter CQAs in future biotherapeutics processes.

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