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Stay on Target: Improving Process Control through Strategic Cascade Feedback Loop Tuning

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BIOPROCESSING

Abstract

Well-developed control strategies are essential for reliable and consistent upstream bioprocess manufacturing. Feedback control loops must be properly engineered to ensure critical process parameters remain within the bounds of defined process limits. Proper control loop tuning ensures that output responses are appropriate and minimal, as excessive system feedback may result in the formation of sub-optimal operational conditions. When control strategies are not well defined, there are increased risks of out-of-specification (OOS) process parameter deviations. Such deviations can negatively impact both process productivity and product quality. Severe OOS results can ultimately lead to final drug substance batch rejection.

Closed-loop proportional-integral-derivative (PID) controllers are commonly used within upstream systems to support robust and effective process control strategies. These PID controllers are often programmed with embedded cascade loops. Unlike single feedback controllers, cascaded controllers can be configured to provide multiple simultaneous system inputs to produce a more elegant process response. This layered feedback approach can help minimize the effects of internal or external process disturbances within bioreactor systems. For optimal performance, cascaded controllers can be customized and tuned to respond most effectively to the unique conditions found within specific upstream bioprocess applications.

In this work, we present an overview of the operation of cascade controllers. We discuss the utility of such systems within upstream bioprocess manufacturing. We then demonstrate this utility with a practical application example. We execute a model process under different sets of cascade configurations and record both the magnitude of pH fluctuations and volumes of pH adjustment media required to maintain setpoint throughout the process duration. Results of this study demonstrate the potential for improved process control though iterative cascade loop tuning. Scientists and engineers might consider adopting the techniques outlined in this study to evaluate and improve cascade feedback control within their own bioprocess applications.

Introduction

Bioprocessing describes the manufacture of biologic products through the cultivation of living cells. To promote optimal cell proliferation and sustain high cell viability cultures, bioprocesses must be monitored and controlled within strictly defined limits. Implementing such strict control can prove challenging due to the complex and dynamic interactions found within in most biological systems.[1]

Bioprocess development is often performed using cost-effective, low-volume, orbital shaker flask (OSF) models.[2] Many of the commercial processes developed in these simple flask models are ultimately transferred to production-volume, stirred tank reactor (STR) vessels. Transferring processes to STR bioreactor systems can accommodate the volumetric requirements of commercial manufacturing. Process scaling from shaker flask models to STR systems also provides development teams with opportunities to engineer more robust levels of control into their processes.[3]

Unlike most shaker flask systems, STR systems often have integrated process analytical technologies (PATs) to continuously monitor online process parameters. These process parame-

ters are identified during process development as operational conditions which have the potential to significantly impact final product quality.[4] PATs provide continuous fundamental insight into the manufacturing process and are a direct reflection of the dynamic conditions within STR systems. The continuous monitoring attribute of PATs supports their use within the closed-loop feedback control strategies commonly used across STR systems.

In closed-loop feedback control, a defined setpoint is applied to a monitored process parameter. Using an integrated PAT sensor, the controller measures the process reading against the setpoint value, the difference being defined as the parameter error.[5] A proportional-integral-derivative (PID) algorithm then modulates the controller output in a manner to reduce this error.[6] The output directly influences system conditions by driving physical inputs into the process to bring the process reading toward setpoint. There are two primary types of closed-loop feedback control systems: single feedback control systems and cascaded control systems.

A single feedback controller drives corrective inputs the system based upon the magnitude of the calculated parameter error.[7] For dynamic systems, where sensors may not be able to respond immediately to internal or external disturbances, single feedback controllers may cause process variables to either undershoot or overshoot the defined parameter range. This inaccuracy can result in the formation of unfavorable or out-of-specification (OOS) operational conditions within the system. The magnitude of such deviations can result in quality excursions that could negatively impact the safety or efficacy of the final product.

Cascade feedback controllers were introduced as a means of improving system performance within dynamic systems. The use of cascade feedback within closed-loop PID controllers allows for the desired setpoint of one controlling unit (master control loop) to be dictated by the control action of one or more others (cascade control loops).[8] The cascaded controller output(s) can be programmed to respond immediately to changes in sensor measurements, even when very little error is observed. Multiple subordinate cascaded controllers can be included within a single master control loop. This structuring supports layered responses that can minimize overshoot and process fluctuation. An example of a closed-loop cascade controller with a single cascaded response is illustrated in **Figure 1**.

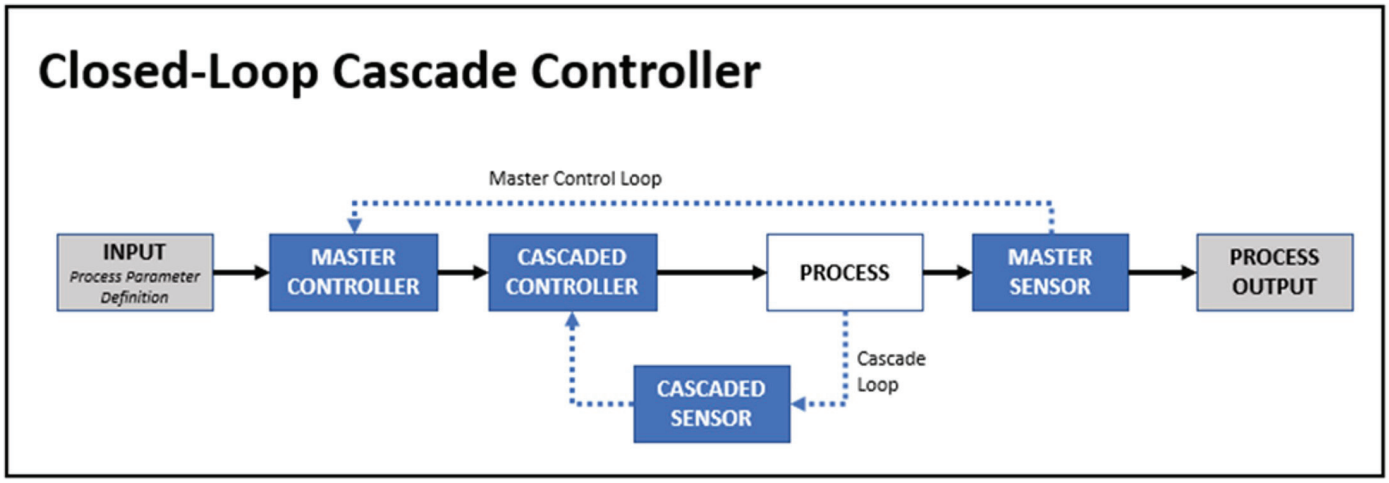

Figure 1: Overview of a closed-loop cascade controller. The subordinate cascade loop is used to directly drive process inputs.

Cascade Control for pH Regulation

Due to its potential to impact both culture health and product quality, bioreactor pH is routinely recognized as a critical process parameter across many upstream manufacturing bioprocesses.[9] Bioreactor pH control feedback loops are typically driven by closed-loop cascade controllers. When programming pH control feedback loops for bioreactor systems, process engineers and scientists should use caution to ensure that controller responses do not introduce excessive control inputs into their bioreactor systems. Such inaccuracies have the potential to negatively impact the operational conditions within cell culture environments.

Bioreactor pH control is typically regulated through either the addition of acid and base solutions or through the direct sparging of carbon dioxide gas into the system. Both of these methods increase osmolality of the media: a colligative property that describes the quantity of dissolved moles of solute per kilogram of solution. For cell culture applications, if the osmolality of a system increases beyond the bounds of the physiological range (275 to 295 mmol/kg), the system can become hypertonic.[10] Hypertonic conditions have been documented to adversely affect the specific growth rates of certain cultures.[11] To reduce the risk of hypertonic conditions being created within upstream processes, bioreactor pH cascade control strategies can be tuned to minimize the transfer of pH adjustment solutions and gases.

Application-specific cascade controller tuning supports output response optimization for pH feedback loops. Cascade controller tuning may be performed in parallel or independent of PID parameter tuning.[12] Similar to PID tuning, effective cascade tuning requires the identification and understanding of the following: control objectives, input variables, output measurements, equipment constraints, and process operating characteristics.[13] The potential for both internal and external disturbances should also be considered when optimizing and tuning cascade feedback control strategies.

In this work, a simulated upstream bioprocess was used as a model to illustrate the benefits of cascade controller tuning. A 5-L bioreactor was operated using a model medium under standard cell culture temperature and agitation process conditions. A continuous addition of low concentration acid was utilized to simulate an internal process disturbance. A pH setpoint step change was performed to replicate an external process disturbance. The simulated process was executed using three types of cascade configurations. The cascade configurations were defined so that each subsequent iteration refined and improved the response of the previous run. Results from this study demonstrate the benefits of properly configuring cascade loops for specific applications in regard to improved overall process control. The increased degree of process control observed for each subsequent cascade configuration demonstrates the potential significance of cascade tuning.

Materials and Methods

A 5-L autoclavable bioreactor (Distek) was utilized as the STR system for this study. The system featured a single right-handed pitch blade impeller, flute sparger (7 × 0.9 mm holes), three baffles, 1/4" sample downtube, 1/4" harvest downtube, resistance temperature detector (RTD) thermowell, and a single 325mm electrochemical pH probe. Bioreactor operation was performed using the BIOne 1250 Dual-Vessel Bioprocessing Controller (Distek).

Nonsterile 30% Phosphate Buffer Solution (PBS) was used as a model medium for all testing conditions. The medium was titrated to a pH of 7.20 (+/- 0.05) prior to each iteration. An online pH sensor was calibrated with pH 7.00 and pH 10.00 buffers prior testing.

During testing, the media temperature was maintained at a setpoint of 37°C +/- 1.0°C. The agitation rate was held constant at 250 RPM (power per unit volume of 27.99 W/m^3). Axial flow direction was upward. A pH setpoint of 7.20 and a pH deadband of +/- 0.1 were used across all testing conditions. 1M sodium carbonate base and 1M citric acid were used as pH adjustment media solutions to maintain pH parameter setpoints during testing.

To simulate an internal disturbance within the model process, 0.1M citric acid was transferred into the system at a continuous rate of 1.5 mL/min throughout the duration of each run. This ad-

dition was programmed independently of the automated pH adjustment media additions. To simulate an external disturbance, a pH setpoint change was also included within the model process. A shift from 7.20 to 7.00 was initiated at the 20-minute mark during operation. Post-pH shift, the model process was allowed to run for an additional 20 minutes to evaluate if the cascade definitions would support the return of the system to a steady state.

Three separate cascade configurations were tested within this study: Configuration A, Configuration B, and Configuration C. Output definitions for Configuration A were designed to simulate an absence of proper control to intentionally produce a runaway cascade response. During a runaway response, cascade outputs are so excessive that the magnitude of overshoot steadily increases as the online readings oscillate around the setpoint, resulting in an unstable system.

Cascade output definitions for Configuration B and Configuration C were defined in a manner to both incrementally resolve the runaway response conditions created by Configuration A, and to improve overall process control. Improvements in process control would be measured by both a reduction in the magnitude of pH parameter oscillations and in a volumetric reduction of transferred pH adjustment media. An overview of definitions for the three cascade configurations used during this study are presented in **Table 1**. The cascade configuration responses are visually depicted in **Figure 2**.

Results and Discussion

Configuration A was intended to serve as a baseline condition that would simulate a poorly engineered, runaway cascade response. As shown in **Figure 3 (A)**, when the model process was executed using the cascade definitions within this configuration, pH fluctuations of approximately 0.15 were observed prior to the pH shift. Following the pH shift, the pH control could not be maintained, as the acid and base pump speeds were configured to ramp too aggressively. The poorly tuned response caused the online pH measurement to overshoot the deadband with increasing error per oscillation, resulting in the creation of a runaway condition. Due to the dramatic pH oscillations observed, the testing was prematurely ended prior to the 40-minute target, as the system was pronounced unstable.

The acid pump cascade was adjusted in Configuration B so that the rate of addition would be significantly slower in response to pH fluctuation. Additionally, the base pump cascade configuration was redefined to support a faster ramp rate in pump speed. As shown in **Figure 3 (B)**, these changes resulted in pH fluctuations of approximately 0.19 for the entirety of the process. Online trends remained within the limitations of the defined pH deadband both before and after the pH shift. The parameters defined for Configuration B appeared to resolve the runaway condition created by the parameters from Configuration A.

Table 2: Baseline and Optimized PID Parameter Definitions.

A.	Output	% Pump	B.	Output	% Pump	C.	Output	% Pump
Acid	0%	0%	Acid	0%	0%	Acid	0%	0%
	-20%	40%		-20%	10%		-20%	8%
	-75%	40%		-75%	10%		-75%	8%
	-100%	50%		-100%	15%		-100%	15%
Base	0%	0%	Base	0%	0%	Base	0%	0%
	20%	50%		20%	60%		20%	15%
	75%	50%		75%	60%		75%	25%
	100%	65%		100%	75%		100%	30%

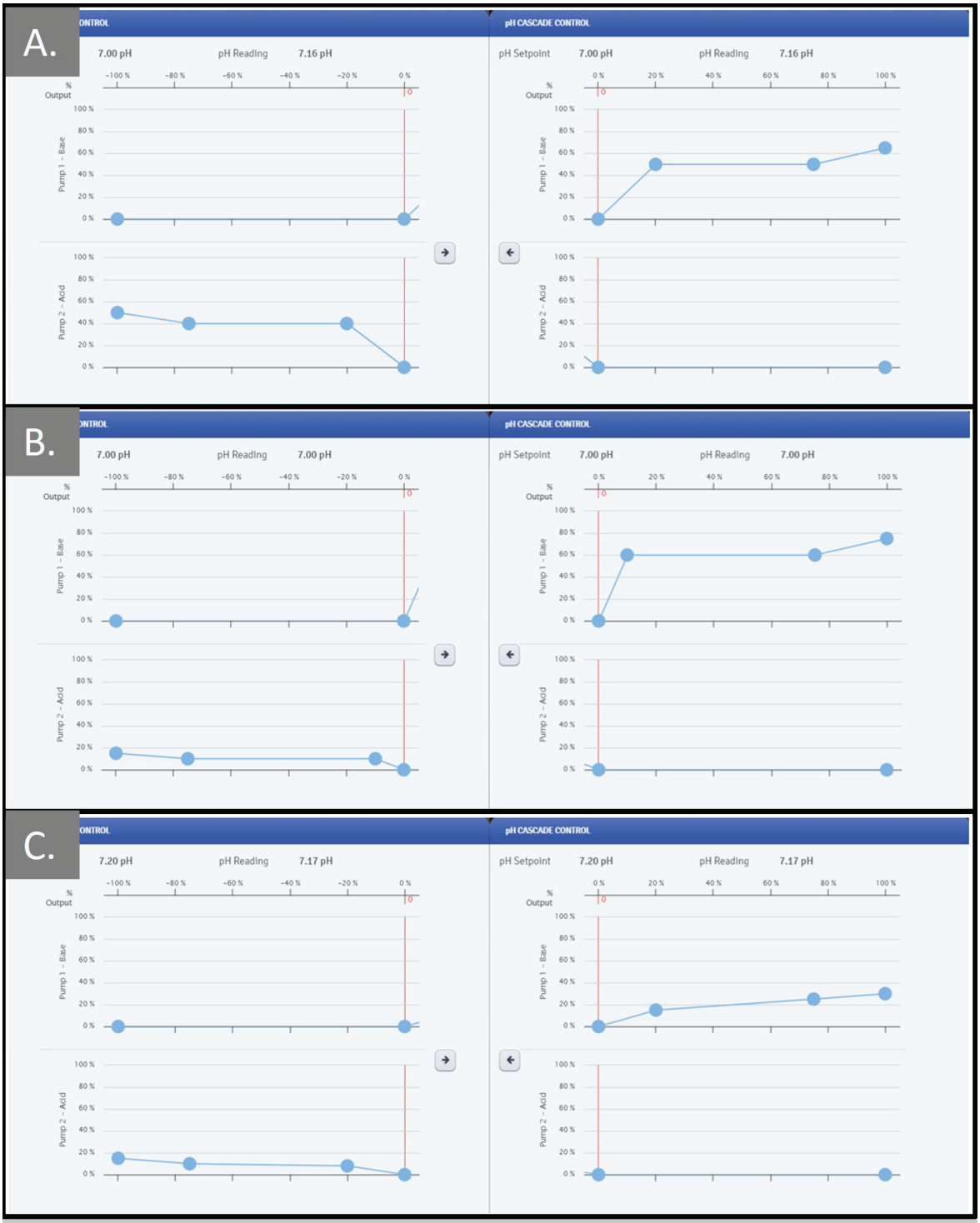

Figure 2: Visualization of the pH cascade configurations tested within this study.

For Configuration C, the rate of base addition was decreased. The goal of this tuning change was to reduce the magnitude of the fluctuations that were observed with Configuration B. Results, shown in **Figure 3 (C)**, demonstrate that this turning was highly effective. The magnitude of pH fluctuation for Configuration C was approximately 0.03, and constant throughout the entirety of the 40-minute duration of the run. It can be observed that the process trend favors the bottom of the deadband for this configuration. This type of response minimizes the addition of pH adjustment media into the system, and is expected for well-tuned cascade strategies.

The totalized volumes of 1M citric acid and 1M sodium carbonate base required for each testing iteration are shown in **Figure 3 (D)**. Examining these data, it is clear how well-tuned cascade strategies can reduce the required volumes of pH adjustment media needed to maintain pH within a bioreactor system. The volumetric totals of pH adjustment media that were added when the process was operated under the Configuration C parameters were approximately 80 - 90% less than the volumes required for the Configuration A parameters. If Configuration A testing was allowed to continue for the entire 40 minutes, this percentage would likely have been even greater. Volumetric totals of pH adjustment media for the Configuration C process were also less than 50% of the volumes required for the process when it was executed under Configuration B parameters. This reduction in required pH adjustment media volumes could theoretically help to maintain system osmolality within ranges more optimal for culture health and productivity. Continued tuning of Configuration C could possibly result in further volumetric reductions in pH adjustment media needed to maintain the defined setpoint range.

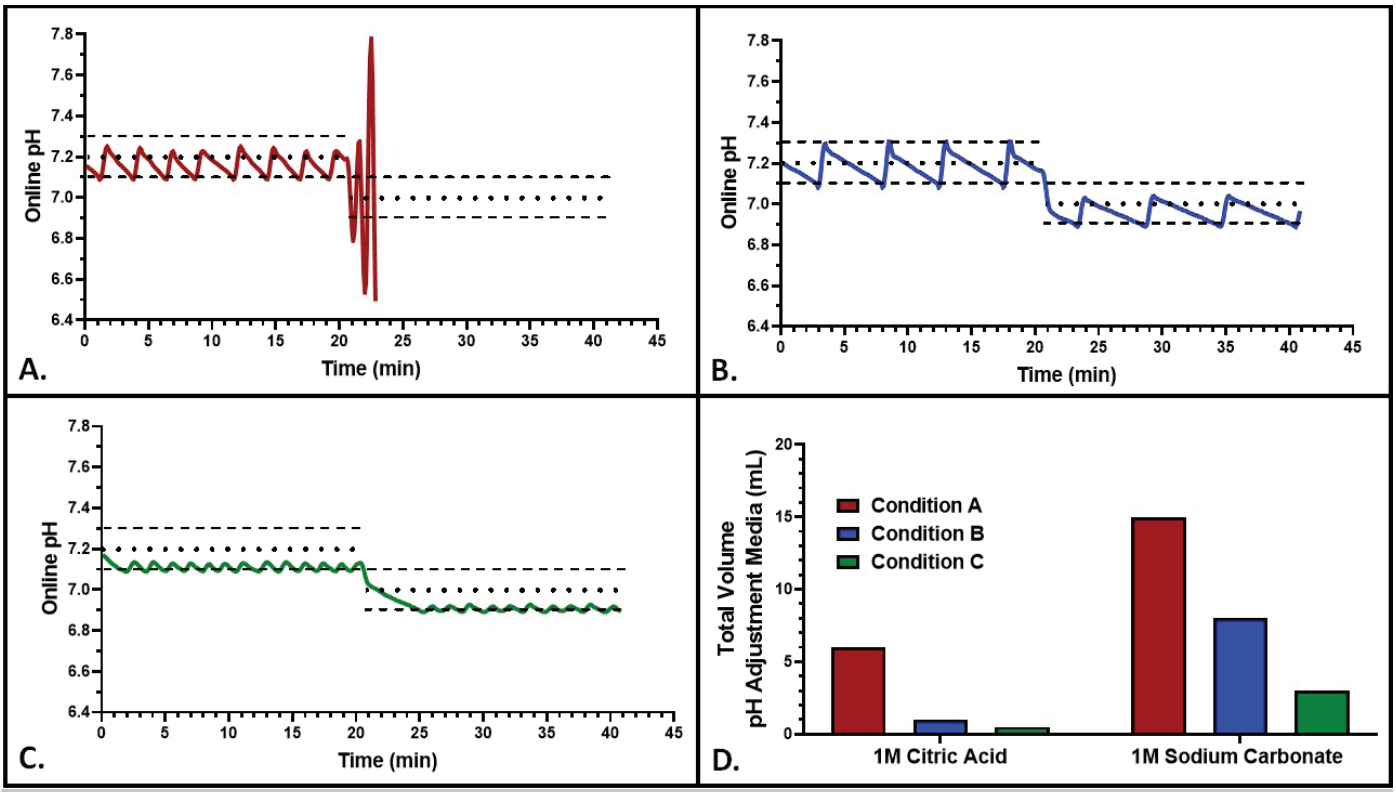

Figure 3: Individual pH data trends for each pH cascade configuration: **(A)** Condition A, **(B)** Condition B, and **(C)** Condition C. Volumetric totals for required pH adjustment media shown in **(D)**. Dotted lines indicate pH parameter setpoint and dashed lines indicate pH parameter deadband. Results demonstrate the potential for process optimization through iterative cascade loop tuning. ***Note:*** *Testing for Condition A was prematurely aborted prior to target 40-minute duration due the observation of runaway cascade response after pH setpoint shift.*

Conclusions

Engineering consistent and robust control strategies into bioprocess manufacturing is required to ensure optimal cell health, productivity, and product quality. Closed loop PID controllers with embedded cascade loops are commonly used in bioprocessing due to the dynamic and non-linear nature of these applications. Cascade controllers consist of a master controller whose output is based on both the reading of an online PAT sensor and one or more embedded cascaded controllers. Cascade controllers are configurable to provide inputs based on the specific nuances of each process. As such, they can help achieve a high degree of process control. Cascade controllers are also able to respond quickly to both internal and external process disturbances. To ensure optimum performance of cascade controllers, each feedback loop should be specifically tuned to best meet the needs of individual process applications.

In this study, an iterative tuning method was performed to optimize a pH cascade for a model process performed within a 5-L autoclavable bioreactor system. Results demonstrated the potential for improved process control through cascade loop tuning. Reductions in pH oscillation magnitude and decreases in required pH adjustment media volumes were both observed after cascade parameters were refined. Both of these responses are favorable and have the potential to support a more optimal cell culture environment. Process scientists and engineers might want to consider utilizing the described cascade loop tuning techniques within this paper to improve their own upstream operational conditions.

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