The Significance of PID Tuning within Biopharmaceutical Processes

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BIOPROCESSING

Abstract

When developing and optimizing bioprocesses, robust and effective process control strategies must be established. Suboptimal control strategies can result in the emergence of process parameter deviations and out-of-specification (OOS) process conditions. Such adverse results can negatively affect culture health, productivity, and overall product quality.

Proportional-Integral-Derivative (PID) controllers are used throughout the biopharmaceutical industry to support robust process control across both upstream and downstream bioprocesses. PID controllers utilize programmable feedback control loops. These control loops regulate process parameters within defined specification limits. For optimal performance, PID controllers often benefit from application-specific tuning. Application-specific tuning of PID parameters helps support manufacturing process consistency and optimal results.

PID tuning is a subject matter which is often unfamiliar and ambiguous to many classically trained biologists and life scientists. As a consequence of this unfamiliarity, many biopharmaceutical laboratory teams operate their controllers with suboptimal PID tuning parameters. In this work, we present a high-level overview of PID tuning principles. The intent of this information is to provide foundational knowledge of the subject matter to support PID tuning efforts within biopharmaceutical laboratories. We conclude this work with a practical example that demonstrates the benefits of PID tuning. In this application example, heating regression PID parameters for a highly complex upstream process model are optimized using a closed-loop feedback tuning method. The resulting process demonstrates the potential for improved process control through the execution of strategic PID parameter tuning.

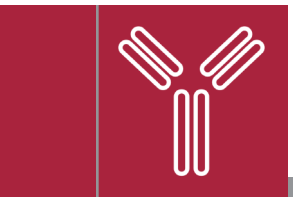
Introduction

Bioprocessing is defined as the cultivation of living cells to produce a desired end product. To promote cell proliferation and sustain high cell viability cultures, environmental conditions within bioreactors must be regulated and maintained within strictly controlled limits. Such control can be challenging due to the non-linearity, variability, and complexity of biopharmaceutical processes.[1]

Efficient and effective process control can be achieved using many available control loop technologies. Such technologies can range greatly in complexity. Feed forward open-loop controllers, where pre-determined inputs are provided to the system, represent simpler versions of such solutions. Artificial intelligence or model-based controllers represent much more intricate options, which can both recognize and adapt to dynamic process conditions.

One simple, yet robust control strategy that is well-established in the biotechnology industry is closed-loop feedback control using Proportion-Integral-Derivative (PID) controllers. These controllers utilize a relatively simple three-parameter algorithm to drive a control output. This approach has been demonstrated to be an effective means of process control, even for highly complex, dynamic bioprocesses.

PID controllers operate through continuous feedback control in which a defined setpoint is applied to a monitored parameter on the controller. Using a sensor, the controller measures



process readings against the setpoint value. The difference between a process reading and a programmed setpoint is defined as parameter error.[2] The three-parameter PID algorithm then modulates the controller output in a manner to reduce this error. The output directly influences system conditions by driving physical inputs into the process. These physical inputs reduce the magnitude of error and drives the process parameter to remain constant at the defined setpoint value.

The three parameters of the algorithm that govern PID controller output are Proportional Gain (k_p), Integral Gain (k_i), and Derivative Gain (k_d). The overall controller output is the sum of the contributions from these three terms. During PID tuning, the values for all three of these parameters can be optimized for specific bioprocess applications.

The proportional gain term (k_p) drives controller output directly proportional to the magnitude of the current system error. A large proportional value will induce a larger controller output response when the error is large. Conversely, a smaller output response will be driven when the magnitude of the error is small. When utilized alone, proportional gain will result in constant output oscillation, where the parameter will be continuously overshooting and undershooting the defined setpoint.[3] An overview of how changing the proportional gain term value can affect control-loop responses is shown in **Figure 1A**.

The integral gain (k_i) drives controller output based upon accumulated past error above and below setpoint, ultimately driving the current error to near zero. The primary purpose for the integral gain response is to reduce continued offset from setpoint. When combined with proportional gain, the integral value will likely drive increased initial setpoint overshoot. However, after this initial overshoot, the magnitude of error will then be systematically reduced with each oscillation.[3] An overview of how changing the integral gain term value can affect control-loop responses is shown in **Figure 1B**.

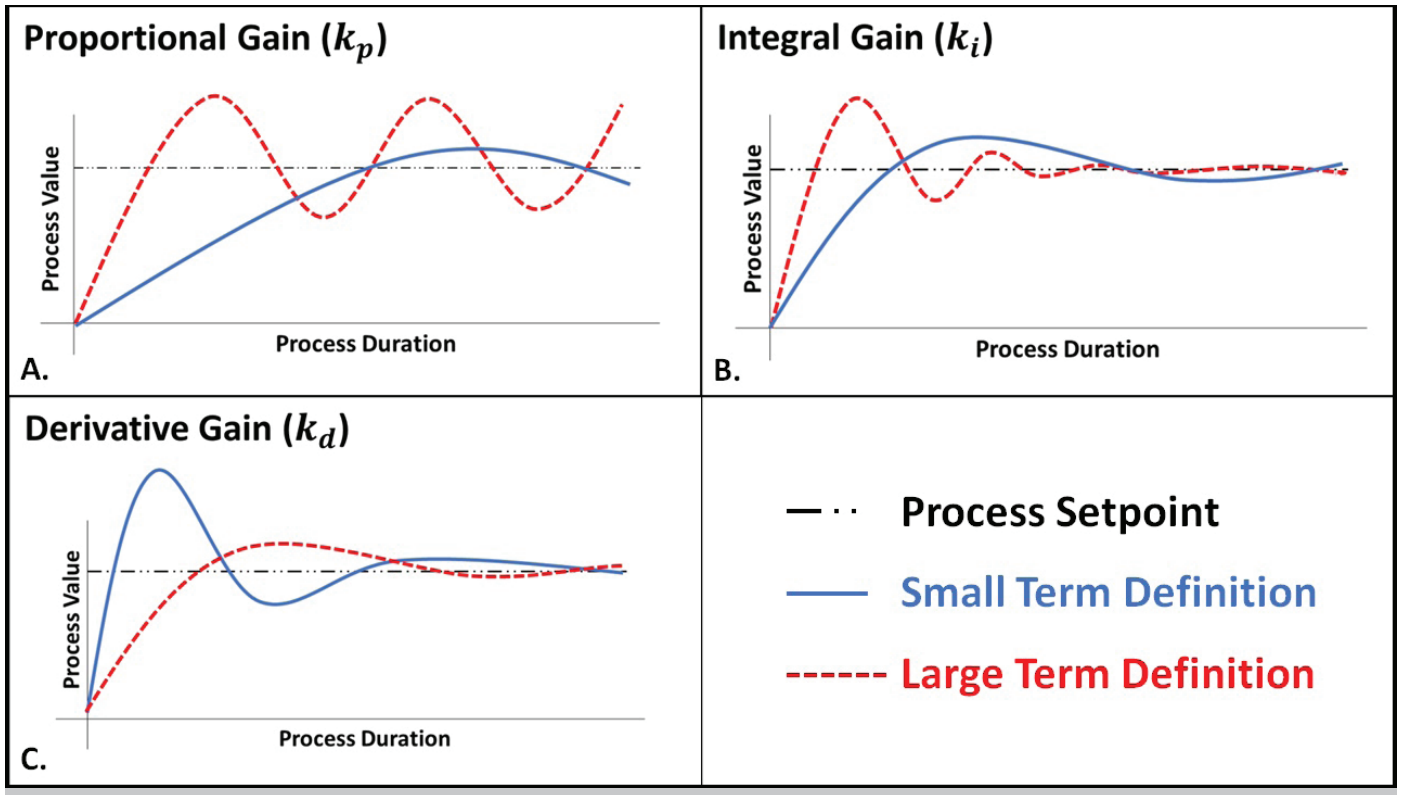


Figure 1: Overview of how changing the definitions of PID term will affect output responses in dynamic systems. **(A)** Effects of increasing proportional term. **(B)** Effects of increasing integral term. **(C)** Effects of increasing derivative term.

The derivative gain (k_d) drives controller output based on the rate of change in controller output in response to error over time. This function is used to either increase the rate of controller response or to improve the stability of the system. When combined with proportional gain and integral gain, an increased derivative value will slow the rate of change in error as the error gets smaller, thus reducing overshoot and oscillation.[3] An overview of how changing the derivative gain term value can affect control-loop responses is shown in **Figure 1C**.

Controller PID tuning describes the process of determining appropriate definitions for each of the proportional gain, integral gain, and derivative gain parameters, as determined by the nuanced requirements of the specific process application. The goal of PID tuning is to create a robust control strategy that supports strict process operation within the bounds of defined setpoint limits. Effective PID tuning requires an identification and understanding of the following: control objectives, process inputs, output measurements, system and equipment constraints, and process operating characteristics.[4] Many PID tuning methods have been described. These methods primarily fall into two main categories: closed-loop tuning methods and open-loop tuning methods.

Closed-loop tuning techniques involve tuning the controller in *Automatic* mode. During closed-loop tuning, stepwise setpoint adjustments are made to process definitions. Direct process feedback measurements are detected by an online sensor. Adjustments to PID parameters are made based upon controller output responses to these measurements.

Open-loop tuning techniques involve tuning the controller in *Manual* mode. During open-loop tuning, direct outputs are commanded to the controller. Process responses to these direct output changes are then measured. PID parameters can then be adjusted as necessary to optimize process responses.[5] The differences between closed-loop and open-loop control strategies are summarized in **Figure 2**.

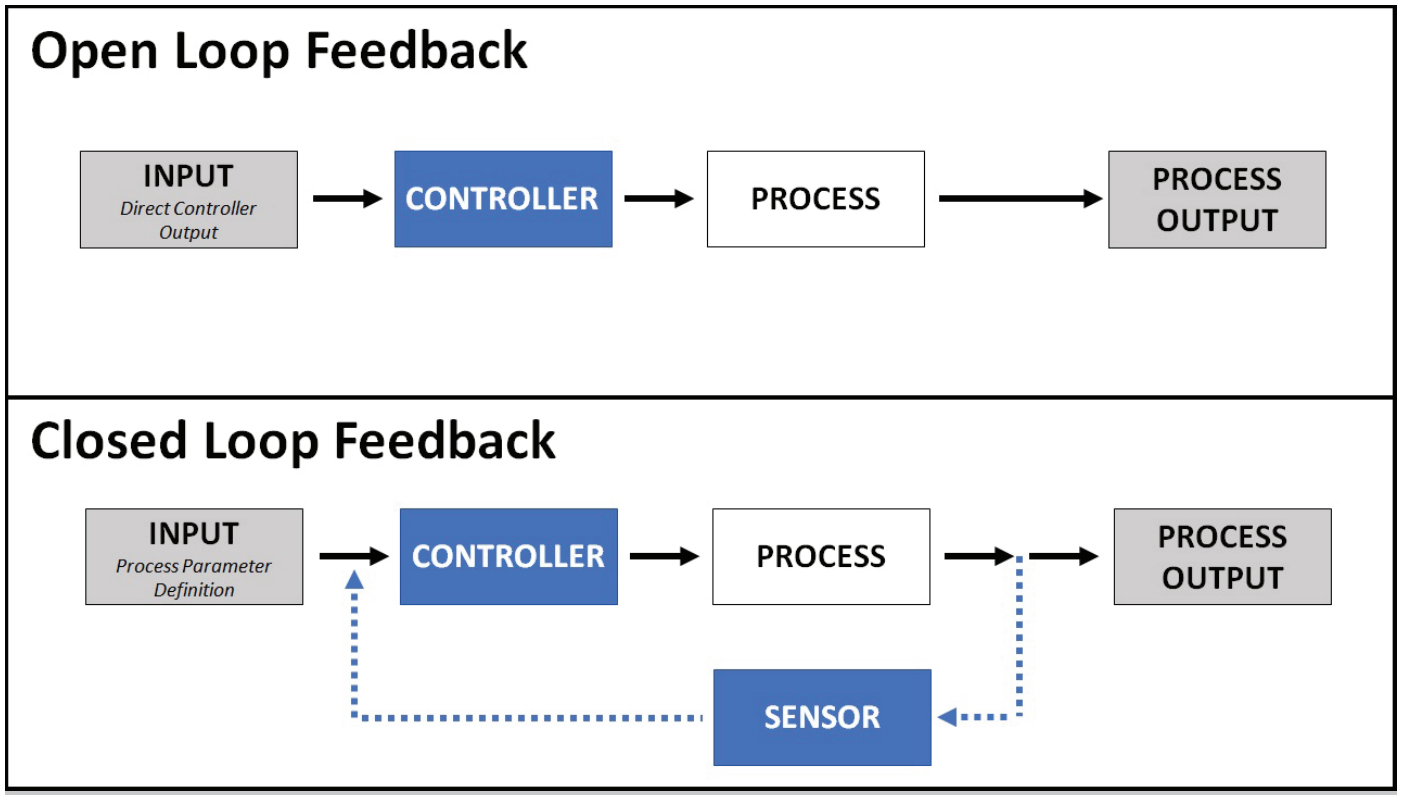


Figure 2: Overview of the closed-loop and open-loop tuning loops. The integration of sensor-driven feedback in the closed loop tuning process distinguished the two methods.

For this work, a closed-loop tuning method was utilized to optimize the PID function definitions for temperature control within a highly complicated upstream process model. Results from this study demonstrate the suitability of this method for decreasing setpoint error and improving overall process control. The improved control strategy demonstrates the potential benefit that strategic PID tuning can have within biopharmaceutical processes.

Materials and Methods

A BIOne Single-Use Bioreactor (SUB) manufactured by Distek was utilized for this study. The specific BIOne SUB evaluated was model number 2022-1006. This model which features a 5-L working volume, a single right-handed pitch blade impeller, and a flute sparger, (7 × 1.5 mm holes). Bioreactor operation was performed using the BIOne 1250 Dual-Vessel Controller, model number 2022-8122.

The Distek BIOne 1250 controllers utilize PID control to maintain temperature, pH, and dissolved oxygen process parameters at defined setpoints. Template recipes for standard microbial and cell culture processes are preloaded onto all BIOne 1250 systems. These recipes include definitions for PID parameters which have been demonstrated to be sufficient to support the requirements for the majority of standard upstream bioprocesses.

It has been recognized that the preloaded PID definitions may not be optimal to support process control for certain unique bioprocesses. For such nuanced applications, further PID parameter tuning can be performed to enhance the overall process control of the system. In this work, we performed this type of optimization on temperature regression PID parameters for a unique upstream bioprocess model that included strict setpoint limitation requirements.

The upstream bioprocess modeled within this study represented what might be used for a microcarrier-based, adherent cell culture, three-dimensional expansion. Compared to traditional suspension cell culture applications, overall system power input per unit volume (P/V) is relatively low for microcarrier-based processes.[6] The decrease in power input is due to the increased risks of potentially cell-damaging microcarrier-to-microcarrier collisions occurring within in the system. Reduced power input decreases the thermal transfer rate within the system. This decreased thermal transfer poses challenges in defining an effective temperature control strategy for the system.

The model process was further complicated with an extended liquid addition. During the process, the working volume was increased from 1500 mL to 3000 mL. Ambient temperature water was added to the system at a rate of 12.5 mL / min. Two temperature shifts were performed in series after the liquid addition phase. Agitation in the system was maintained at 100 rpm for all phases (P/V = 2.39 W/m^3 to 4.78 W/m^3). An overview of the entire model process used for the PID parameter optimization study is shown in **Figure 3**.

Strict temperature setpoint limits were defined for the entirety of the process. During the initial heat-up and temperature shift phases (Phase 1, 3, and 4), a range of +/- 1.0°C from setpoint for initial oscillation. During the liquid addition portion (Phase 2) of the model process, the temperature specification range was tightened to a range of +/- 0.2°C from setpoint.

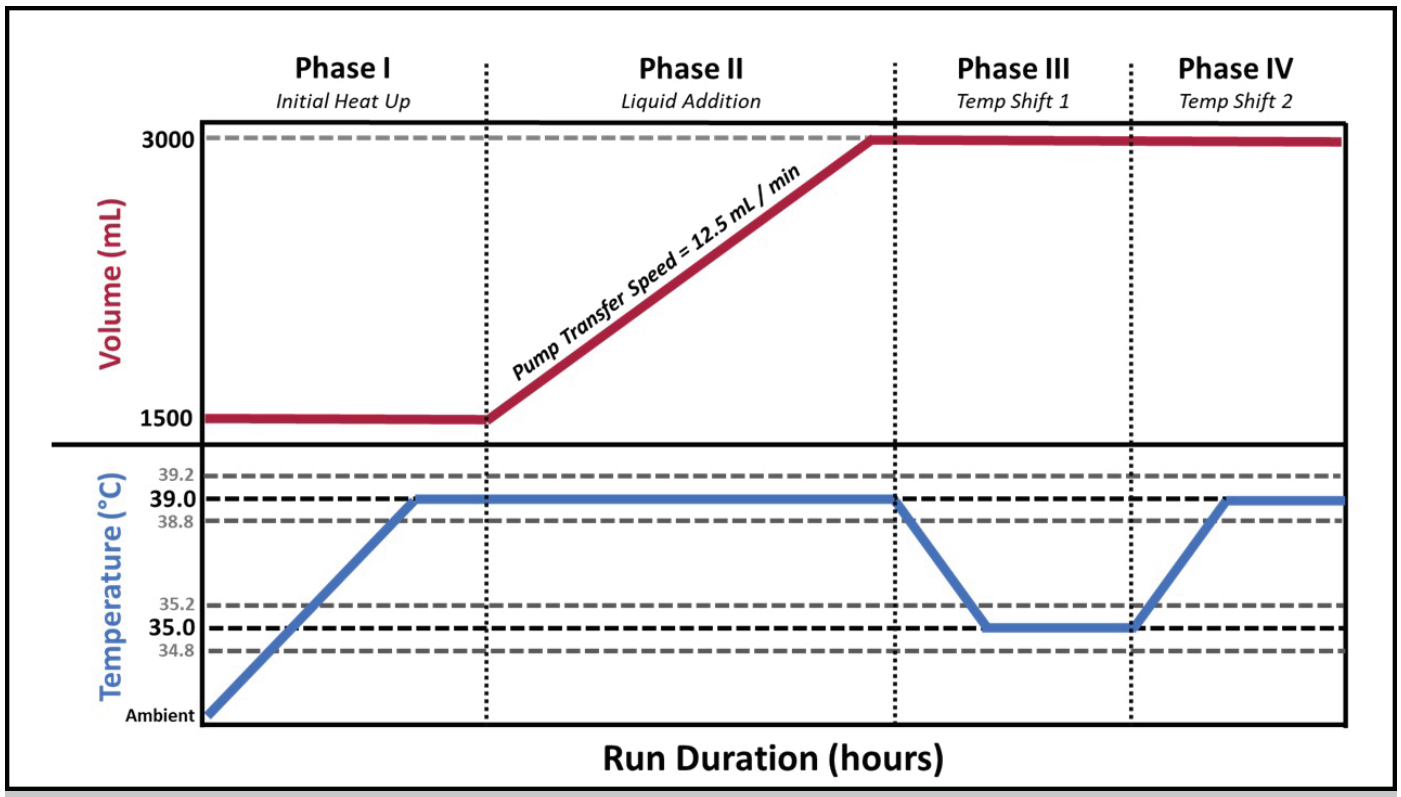
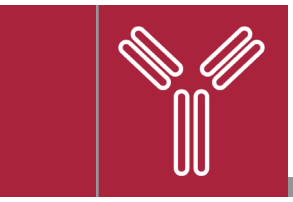


Figure 3: Model process used for PID optimization study. Temperature parameter limits were defined as +/- 0.2°C from setpoint during liquid addition (Phase II) and +/- 1.0°C from setpoint for initial oscillation during temperature shifts (Phases I, III, & IV).

To optimize the PID definitions for the process, an iterative Ziegler-Nichols tuning method was utilized to optimize the PID parameters. Using the tuning method, the system was first controlled at a fixed temperature set point of 39.0°C with the Integral Gain (I) and Derivative Gain (D) set to zero. The Proportional Gain (P) was then incrementally increased from zero via iterative testing until it reached the Ultimate Gain (K_u), at which the output of the control loop had stable and consistent magnitude oscillations. The Ultimate Gain and Oscillation Period (T_u) were then used to determine the P, I and D parameters per the equations in **Table 1**, which target minimal overshoot and slow controller response.[7]

Table 1: PID Parameter Tuning Equations.

PID Parameter	Equation
Proportional Gain (P)	$0.33 * K_u$
Integral Gain (I)	$0.66 * \frac{K_u}{T_u}$
Derivative Gain (D)	$0.11 * K_u * T_u$



Once the initial P, I and D parameters were determined for steady state temperature control, a trial-and-error iterative tuning method was used to further refine the PID parameter definitions, particularly for the extended liquid addition portion of the process. Once tuning was completed, the model process was then executed in its entirety with the optimized definitions. The baseline and optimized PID definitions parameters used during this study are presented in **Table 2**.

Table 2: Baseline and Optimized PID Parameter Definitions.

Parameter	Baseline Tuning Definition	Optimized Tuning Definition
Proportional Gain (P)	0.25	0.41
Integral Gain (I)	0.4	0.35
Derivative Gain (D)	6	0.27

Results and Discussion

The overall temperature and volumetric trend data from the two iterations of the model process that were executed using either the baseline or the optimized PID definitions are shown in **Figure 4**. The four individual process phases are presented with higher resolution in **Figure 5**. In this figure, highlighted temperature specification ranges are included for reference for each process phase. These data demonstrate that both the baseline and optimized conditions were able to meet the defined temperature specifications for overshoot during the initial heat up (Phase 1) and temperature shift (Phase 3 & Phase 4) portions of the process (specification was defined as +/- 1.0°C from temperature setpoint). However, it should be noted that during the heating portions of the process (Phases 1 & 3), the optimized conditions allowed the setpoint to be reached 0.2 – 0.3 hours faster than the baseline tuning conditions. Such improvement in heating efficiency is typically viewed as a favorable response. The improved heating efficiency observed was likely due to the increased proportional gain value within the optimized PID parameters. No such difference was noted during the cooling temperature shift from 39°C to 35°C. This is likely because system cooling was performed passively during the study with no cooling water input. The rate of cooling was driven only by the gradient between the atmospheric and internal bioreactor temperatures. Therefore, the rate of cooling would not be influenced by the definitions of the PID terms.

The baseline PID tuning parameters could not support the defined temperature specifications for the liquid addition portion of the process (Phase 2). During the entirety of the two-hour liquid addition, the temperature of the system was outside of the defined specification range (+/- 0.2°C from setpoint) using the baseline PID tuning. These results were greatly improved upon through the use of the optimized tuning parameters. Using optimized PID parameters, the temperature only deviated from the specification range for approximately 0.3 hours. After this brief deviation time, the temperature then remained within the specification range for the remainder of the liquid addition. The reduced deviation time was likely due to a combination of the increased proportional gain term and decreased derivative gain term within the optimized PID definitions. It is believed with further process refinement (i.e., decreasing the rate of addition or slightly increasing the temperature of the liquid), this process could be completely optimized so that no deviation would be observed during future iterations executed with the optimized PID term definitions.

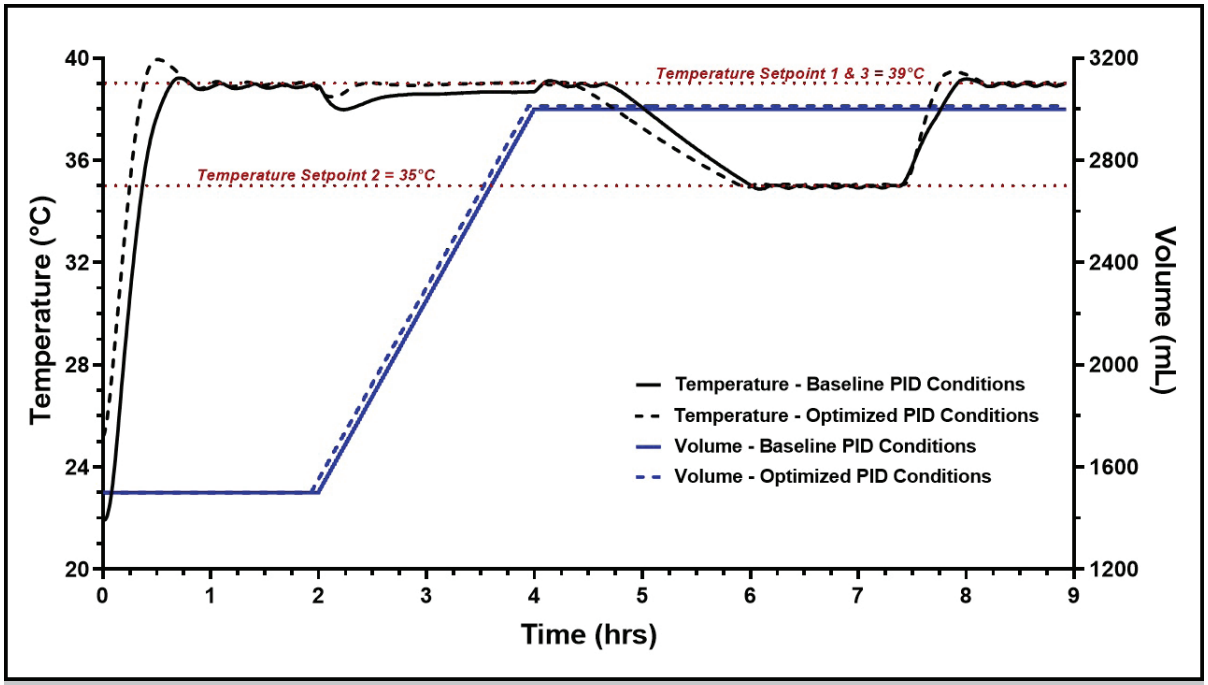


Figure 4: Overview comparing volumetric and temperature data trends from separate process iterations executed with either baseline or optimized PID term definitions.

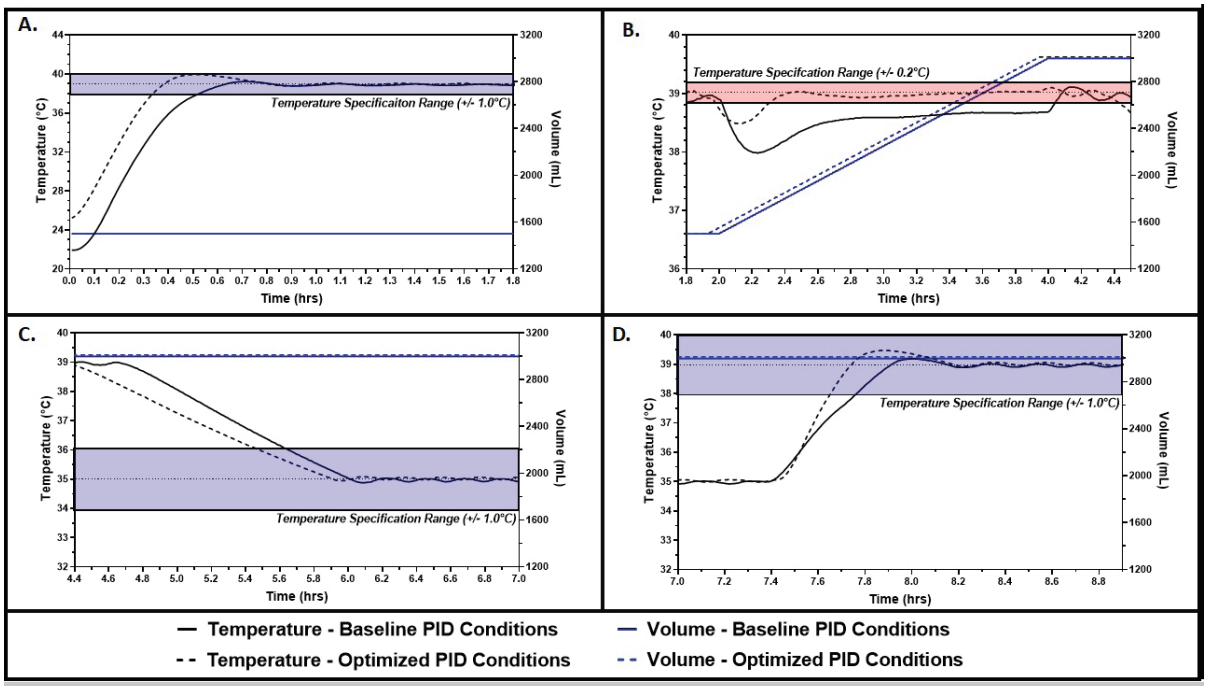


Figure 5: Model process used for PID optimization study. Results demonstrate the potential for process improvements from optimized PID definitions. **A**. Phase 1 of process (Initial Heat-Up). **B**. Phase 2 of process (liquid addition). **C**. Phase 3 of process (Temperature Shift 1: 39°C – 35°C). **D**. Phase 4 of process (Temperature Shift 2: 35°C – 39°C).

Conclusions

Both a thorough understanding of the manufacturing process and a means to control that process are necessary for engineering consistency and robustness into any bioprocesses. Strict process control can be achieved through the integration of PID controllers. In order to maximize the effectiveness of such controllers, application specific PID parameter tuning is often required. However, due its inherent complexity, PID tuning is not frequently performed by many biopharmaceutical laboratory teams. Through this work, we both explained the fundamentals of PID tuning and demonstrated the value of such an endeavor for enhanced process control.

Using a closed-loop PID tuning method, we were able to optimize the temperature control PID tuning parameters on the BIOne 1250 controller for a 5-L SUB system. The optimized definitions improved the heating regression rate within the system. Additionally, the integration of these definitions demonstrated improved setpoint control during an extended liquid addition portion of the process. As we have demonstrated in this work, such tuning methodology can be a valuable tool for scientists to help drive process optimization and demonstrate superior process control.

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