Simplifying Progress

Pionic® Spin: An Advanced Solution for Robust and Precise Continuous Virus Inactivation

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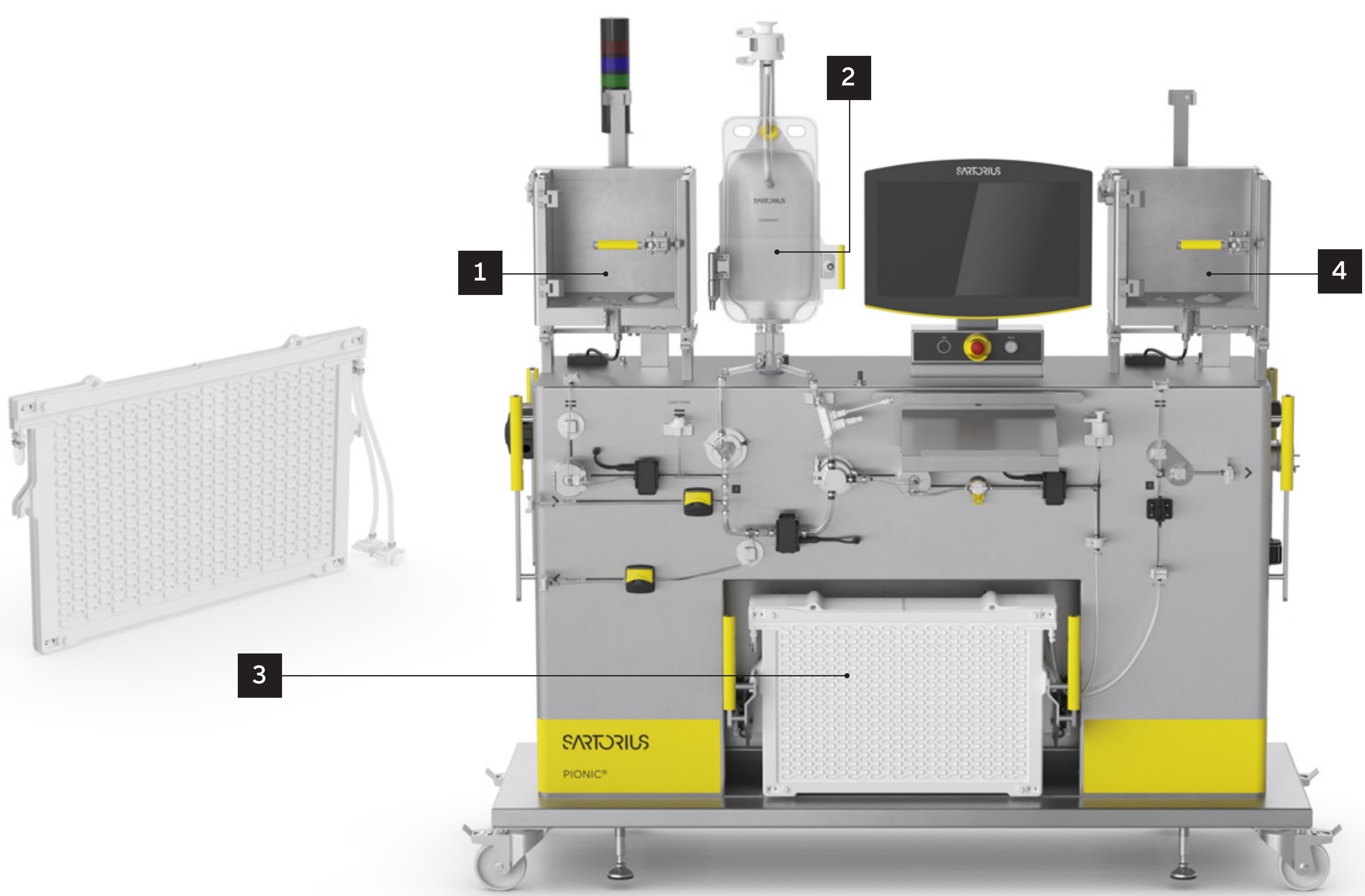
Abstract

The shift from traditional batch processing to integrated continuous biomanufacturing is transforming the production of biopharmaceuticals by significantly increasing efficiency, reducing costs, minimizing facility footprint requirements, and lowering environmental impact. Pionic® Platform enables modular, automated solutions for intensified continuous biomanufacturing, including robust and effective virus inactivation at low pH with Pionic® Spin.

Pionic® Spin addresses key challenges in virus inactivation through homogeneous acid-feed mixing and precise pH control. This white paper focuses on how the engineering of the recirculation loop, dynamic mixing strategies, and advanced pH control using process-specific titration curves support robust and regulatory-compliant virus inactivation.

Figure 1: Pionic® Spin comprises four functional zones: **(1)** homogenization of the feed, **(2)** acidification of the homogenized solution, **(3)** incubation for continuous virus inactivation, and **(4)** neutralization.



Introduction

In response to the growing demand for high-quality biopharmaceuticals, traditional batch processing is increasingly replaced by higher levels of process intensification (PI) with the goal of achieving integrated continuous biomanufacturing (ICB). The transition to higher levels of PI and automated continuous production processes improves efficiency and cost-effectiveness while reducing production times, facility space requirements, and the environmental footprint, including water and carbon emissions.

Pionic®, a novel Sartorius platform, is a key driver in facilitating the biopharmaceutical industry's shift toward ICB. Pionic® modules encompass the downstream process from capture to ultrafiltration (UF) and | or diafiltration (DF), enabling up to level 3 ICB: a fully automated continuous downstream processing platform with autonomously operating, interconnected modules.[1,2] Importantly, individual units from Pionic® Platform can be seamlessly integrated into existing downstream processes, enabling a stepwise transition from batch processing to the desired level of ICB.

Pionic® Spin is an advanced solution for continuous virus inactivation (cVI) at low pH. Designed to support long-term, perfusion-based processing, Pionic® Spin allows continuous operation for up to 28 days without the need to replace ready-to-use components or process analytical technologies.[3]

Pionic® Spin enables efficient and reliable cVI through four functional zones that operate in parallel at constant flow rates during continuous processing (Figure 1). The incoming feed is collected and mixed in functional zone 1, the homogenization bag. In functional zone 2, comprising the recirculation loop and bag, the feed is acidified to the target pH. Functional zone 3, Pionic® Spin Incubator, maintains the acidified feed stream at low pH for at least 30 minutes, achieving a regulatory-compliant virus reduction of ≥ 5 log reduction values. Finally, in functional zone 4, the neutralization bag, the acidified feed is adjusted back to neutral pH, completing the cVI process and preparing the product for further downstream processing.

This white paper outlines the technical solutions utilized by Pionic® Spin to address a key challenge in cVI, with a focus on ensuring uniform acid-feed mixing and consistently reaching the target acidic pH setpoint. These two parameters are essential for effective cVI and must be reliably controlled within functional zone 2, which includes the recirculation loop and the bag.

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Operating Principle of the Recirculation Loop and Bag

Before detailing how homogeneous acid-feed mixing and pH setpoint control are achieved, it is essential to understand the operating principle of the recirculation loop and connected 2D bag (Figure 1) where the acidification takes place.

The recirculation loop and its connected 2D bag form a recirculation circuit through which the feed circulates while entering Pionic® Spin Incubator. A load cell determines the filling level of the recirculation bag based on weight. This information is used to regulate the inflow of additional feed from the homogenization bag and to dynamically adjust the recirculation pump, ensuring homogeneous mixing through precise control of the appropriate recirculation flow rate.

Automated pH titration to the acidic setpoint is facilitated through a combination of conventional feedback and advanced disturbance control, enabled by two pH sensors located in the recirculation loop and in the homogenization bag. Together, these two control mechanisms achieve a precise pH control that maintains the target pH with a control accuracy of < 0.1 pH units.

For simplicity, only the recirculation loop is referenced from this point forward, although functional zone 2 technically comprises both the loop and the bag, which together form the recirculation circuit.

Consistent and Uniform Acid-Feed Mixing

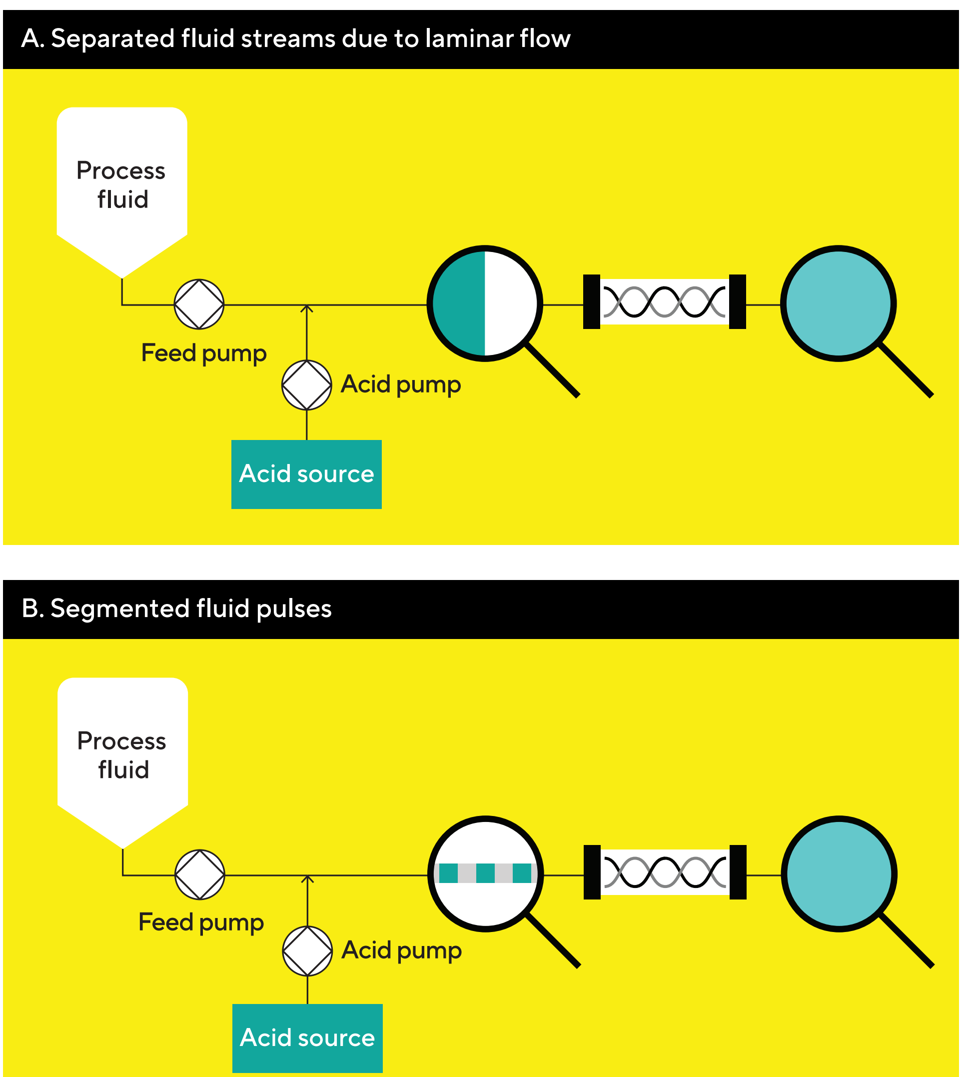
In a continuous downstream bioprocessing system for low-pH virus inactivation (VI), introducing acid into the feed stream presents specific challenges that can compromise process consistency and control. These challenges originate from the inhomogeneous properties of Protein A eluates: product concentration, pH, and conductivity change across the elution peak, complicating the maintenance of steady-state conditions during low-pH virus inactivation. Consequently, the process benefits from a surge tank to pool and blend the eluates. The homogenization bag of Pionic® Spin ensures homogeneous feed mixing and creates ideal starting conditions for dosing the acid within the recirculation loop.

When acid is added via a T-junction into a laminar flow system, insufficient mixing can result in parallel fluid streams (Figure 2A), which may compromise product quality due to localized regions of very low pH at the acid-feed interface. Additionally, pulsed acid addition can lead to segmented pH differences (Figure 2B), further impairing mixing efficiency. These non-uniform pH distributions can be mitigated by incorporating a static mixer equipped with stationary blades or elements that induce turbulence and promote homogeneous mixing (Figure 2A).

In contrast, in the recirculation loop, turbulence is generated by circulating the feed through the loop, driven by the recirculation pump. The recirculation flow is substantially higher than the feed flow rate to enable fast distribution within the loop. Upon entering the recirculation bag, the stream rises to the top and spreads across the surface, carrying nearby fluid. The induced circulation and shear-driven turbulence rapidly mix the liquid throughout the tank.

The described recirculation loop setup offers significant advantages over the conventional addition via a T-junction, which will be described in the following sections.

Figure 2: Schematic illustration of challenges in pH distribution when acid is introduced into a feed stream. In a laminar flow system, acid addition can create parallel pH differences due to fluid layering **(A)**, further influenced by variations in fluid density. Homogeneous mixing can be achieved by generating turbulence, e.g. using a static mixer. Pulsed addition of acid into a laminar feed stream can lead to segmented pH differences **(B)**.



Robust Maintenance of the Acidic pH Setpoint

"The design of the recirculation loop plays a key role in maintaining process stability as it enhances system robustness."

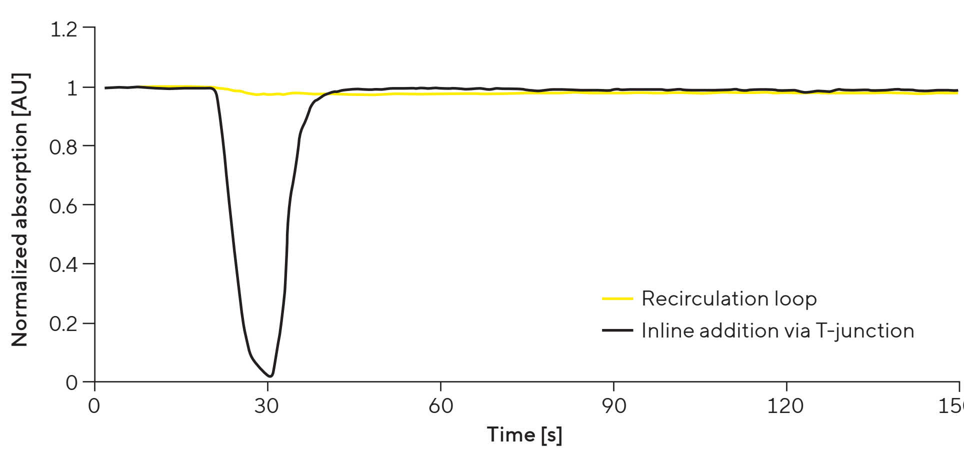
Homogeneous acid-feed mixing is critical for ensuring uniform acidification and, consequently, process stability and robustness. This uniformity is indispensable for achieving and maintaining the acidic pH setpoint throughout the entire feed stream. The design of the recirculation loop plays a key role in maintaining process stability as it enhances system robustness by damping short-term fluctuations in acid addition or feed pH.

Figure 3 depicts the tracer concentration in the recirculation loop following a simulated acid addition disturbance, in comparison to an inline titration system via T-junction. In this experimental setup, optical measurement of a tracer dye was chosen for its higher sensitivity and faster response time compared to pH measurement. To simulate a disturbance, dye addition to the feed was temporarily halted for 10 seconds, while inlet and outlet feed flow were steadily maintained. The impact of this interruption was monitored using a UV sensor.

In the inline titration system, an interruption in dye (acid) addition led to a sudden decrease in UV absorbance, reflecting a sharp pH shift during practical application (black line). This occurs because the temporary halt in dye flow causes a segment within the feed stream where no acid was introduced.

Unlike the inline titration system, the unique design of the recirculation loop provides exceptional and inherent robustness against such disturbances, with the interruption causing only a minor deviation in UV absorbance (yellow line). This robustness is facilitated by the volume of the recirculation loop, which increases system inertia, enhancing resistance to fluctuations and enabling more controlled coloration (acidification).

Figure 3: Comparison of process robustness between an inline titration system and the recirculation loop in maintaining pH stability under disturbance conditions.



Note: A 10-second interruption in dye addition causes a significant drop in UV absorption in the inline titration system (black). In contrast, the unique design of the recirculation loop enhances process robustness against pH disturbances, as demonstrated by the minor decrease in UV absorption in response to the same disturbance (yellow).

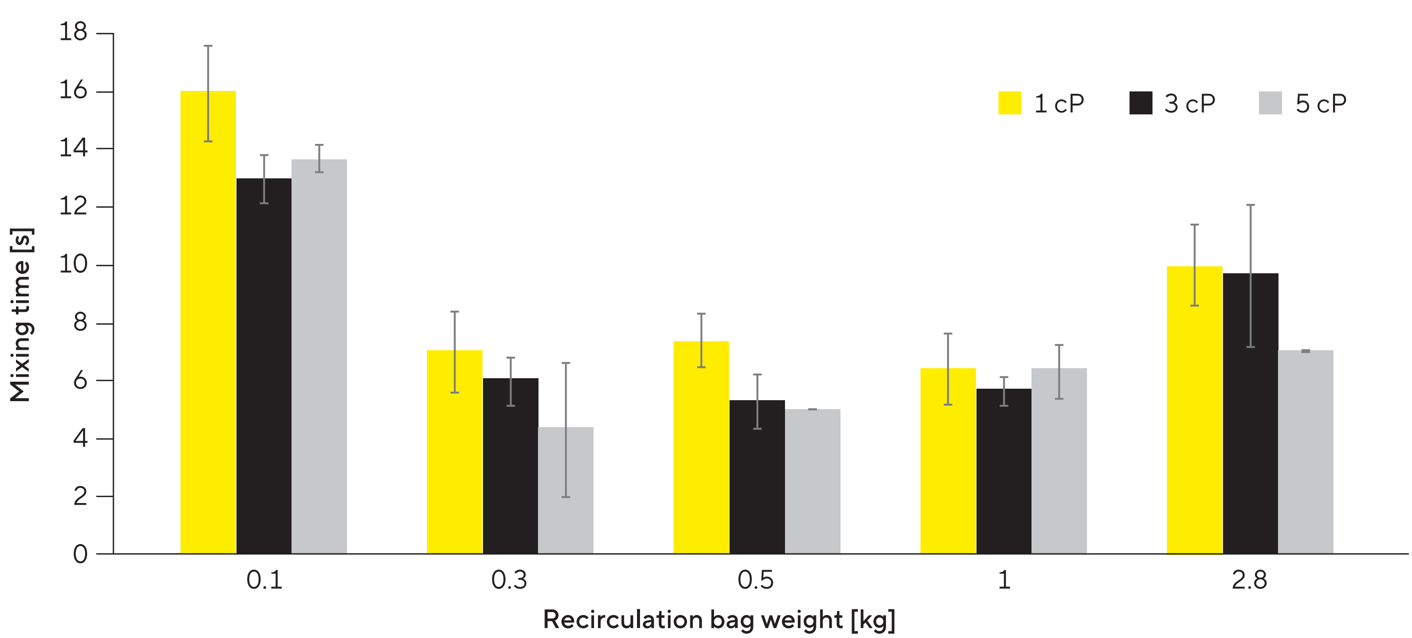
Since electrochemical pH sensors typically have response times of several seconds to a minute, they are less effective at detecting rapid pH changes. Consequently, for inline titration systems, it cannot be guaranteed that rapid pH changes will be reliably detected. By damping fluctuations in acid addition or variations in the feed pH from various consecutive eluates, the recirculation loop ensures stable, consistent acidification and allows accurate pH measurement even in the presence of transient disturbances.

Fast, Efficient, and Consistent Homogeneous Mixing Across All Process Scales

Pionic® Spin achieves optimal mixing performance through dynamic, stepless weight-dependent adjustment of the recirculation flow within the recirculation loop. At low fill levels (low weight), reduced pump speed minimizes foam formation, while at higher fill levels (high weight), increased speed ensures fast mixing.

Figure 4 presents the mixing times for varying recirculation bag weights (0.1–2.8 kg) and viscosities (1, 3, and 5 cP) to mimic different protein concentrations. Above 0.3 kg, the system achieves complete homogeneity in under 10 seconds, demonstrating consistent results regardless of the processing scale. Even for the minimum bag weight of 0.1 kg, the maximum mixing time is 16 seconds. For a given fill level, the mixing time varied by less than three seconds across all tested viscosities.

Figure 4: Mixing times in the recirculation loop. Dynamic, weight-dependent homogeneous mixing enables rapid mixing (below 20 seconds) across a broad range of recirculation bag volumes (0.1–2.8 kg) and viscosities (1, 3, and 5 cP), demonstrating consistent performance under varying process conditions.

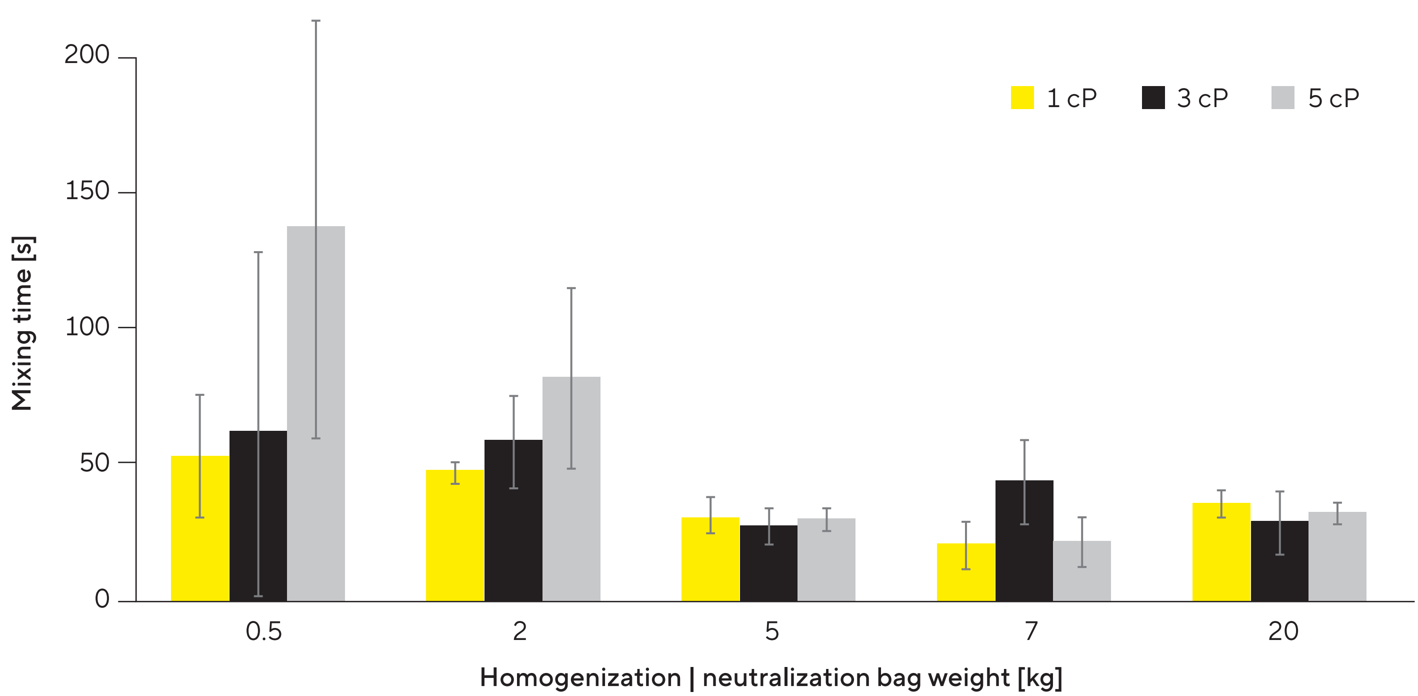


The same principle is applied to homogenization and neutralization bags, with the active mixer speed adjusted accordingly to ensure fast and efficient homogenization. In the homogenization bag, eluates from various cycles of the upstream chromatographic system will be homogenized before entering the recirculation loop. This additional step enables consistent pH adjustment, as the incoming stream has virtually constant fluid properties.

In the neutralization bag, the processed feed must be consistently neutralized, as residual acidity can compromise product integrity. Moreover, the subsequent downstream unit may require a consistently neutral pH to ensure optimal performance and uninterrupted process continuity. This is particularly critical in ICB systems, where the interaction between downstream processing units is fully automated and the feed flows continuously from one unit to the next.

The results of the mixing time determination for the 3D bags demonstrate that, for bag weights higher than 2 kg, the system can achieve complete homogenization of the solution within less than 60 seconds, regardless of the viscosity (Figure 5). At low fill levels (0.5 kg bag weight), complete homogenization within 60 seconds is achieved for viscosities of up to 3 cP.

Figure 5: Mixing times in homogenization and neutralization bags. Dynamic, weight-dependent homogeneous mixing enables rapid mixing (below 60 seconds) for fill levels above 2 kg across different viscosities (1, 3, and 5 cP), demonstrating consistent performance under varying process conditions.



Key Advantages of the Recirculation Loop

The key advantages of the recirculation loop implemented in Pionic® Spin are summarized in Figure 6. The design of the recirculation loop ensures high process robustness in maintaining the acidic pH setpoint, even under challenging conditions such as variations in feed pH. Its adjustable working volume allows for flexible adaptation to specific process requirements. Notably, the loop can be operated at very low working volumes without compromising mixing performance, consistently minimizing exposure time to acidic environments.

Rapid and efficient homogeneous acid-feed mixing is achieved through the dynamic, stepless weight-dependent control of the recirculation pump speed, ensuring consistent performance across varying process scales and viscosities.

Despite facilitating robustness against pH fluctuations and consistently ensuring homogeneous mixing based on filling level, the recirculation loop is also designed to handle pH deviations. If the pH drifts outside the specified limits during continuous operation, the loop will be automatically isolated to recirculate the product within the loop, allowing for correction without requiring product disposal. During this readjustment phase, the outlet valve to Pionic® Spin Incubator remains closed while acid or feed will be added to readjust the pH value to the target specification. Its low hold-up volume ensures that no product with incorrect pH enters the incubation chamber, safeguarding the viral mitigation performance of the entire batch.

Figure 6: Summary of the key advantages of the recirculation loop and bag

Process robustness

- Improved pH robustness compared with inline acid addition via T-junction
- Loop volume can be adjusted to the flow rate and process needs

Mixing performance

- Fast mixing performance with a centrifugal pump
- Automatic adaptation to bag weight avoids foaming

Easy readjustment

- Out-of-specification solutions can be readjusted easily
- Minimal product loss

Minimum hold-up volume

- Low working volume without performance loss
- No dead zones ensure effective inactivation

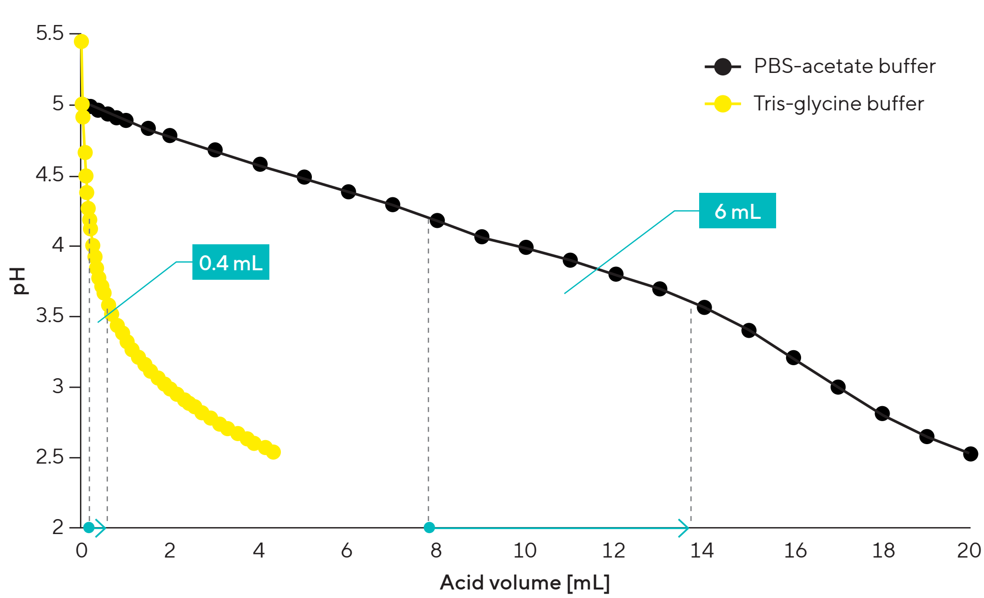
Precise pH Control From the First Elution Cycle

While the previous section focused on the design of the recirculation loop to ensure homogeneous mixing and robustness against pH fluctuations, this section discusses the pH control system, which is essential for accurate titration and maintaining a stable acidic pH within the loop. Precise pH control is critical in low-pH VI, as it ensures process effectiveness. Furthermore, reliable neutralization is essential to maintain product quality and prepare the material for the subsequent processing step.

The buffer capacity of the feed, along with the type and concentration of the acid used for acidification, determine the amount of acid required to reach the target pH. As shown in Figure 7, a Tris-glycine buffer requires less than 1 mL of 0.2 M HCl to reduce the pH from 4.2 to 3.6, while PBS-acetate buffer — which exhibits a higher buffer capacity — needs approximately 6 mL of the same acid concentration to achieve a similar shift. This example clearly illustrates the substantial differences in buffer requirements between individual cVI processes when adjusting the feed to acidic or neutral pH conditions.

In standard configurations, PID controllers are used for pH adjustment. However, qualifying the pH control system for a specific cVI process is time- and resource-intensive, and valuable product is consumed during implementation, reducing production efficiency and increasing total process costs.

Figure 7: Titration curves for two buffer solutions with low and high buffering capacities (Tris-glycine buffer and PBS-acetate buffer, respectively) highlight the difference in acid volume (0.2 M HCl) required to achieve a pH shift to the same target value.



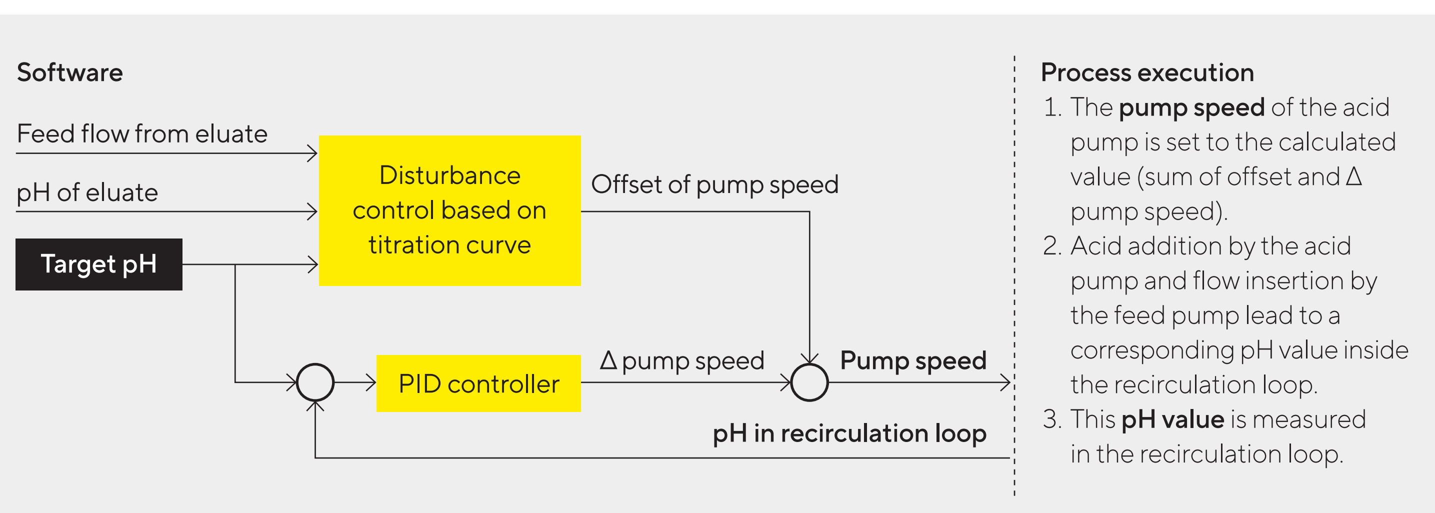
Pionic® Spin overcomes this challenge by utilizing a process-specific titration curve. This curve is generated by titrating a single Protein A elution fraction to both the acidic and neutral pH setpoints. Alternatively, existing titration data from a previous batch can be applied. The data is integrated into the pH control system, which combines two control loops: well-established feedback and innovative disturbance control. Both are used to control the acidic and neutral pH setpoints.

The disturbance control calculates the pH difference between the incoming feed and the target pH setpoint (acidic or neutral), while the feedback control monitors the deviation between the current pH and the target value. Three pH sensors enable both acidic and neutral pH control. For acidic pH control, one sensor is located in the homogenization bag and the other in the recirculation loop. For neutral pH control, the disturbance control uses the sensor in the recirculation loop, while feedback control relies on a sensor located in the neutralization bag.

Biobrain® software compares the feed pH deviation detected by the disturbance control to the titration curve to predict the exact acid or base volume required to reach the target pH. This predictive dosing is then combined with real-time signals from both control loops. Biobrain® software sums the predictive signal from the disturbance control and the corrective signal from the feedback control to calculate the final acid or base demand (Figure 8). It then adjusts the pump speed accordingly to deliver the precise volume of acid or base solution.

This innovative pH control approach enables fast, precise, and robust pH adjustment, even under dynamic process conditions such as fluctuations in the incoming feed pH from various eluates or changing feed flow rates. The titration curve also eliminates time-consuming test runs, ensuring reliable and efficient cVI processing from the first application.

Figure 8: Schematic illustration of the pH control system utilized in Pionic® Spin. Two control loops, feedback and disturbance control, ensure precise pH control in both the recirculation loop and the neutralization bag. The disturbance control is supported by a process-specific titration curve, enabling predictive acid | base dosing.



Conclusion

Low-pH virus inactivation is a critical risk mitigation step in the production of biopharmaceuticals. It is essential for assuring viral safety of the final product, which is required by regulatory authorities.

Homogeneous mixing and precise pH control are key challenges in VI, particularly when VI is performed in a continuous process where steady-state flow rates make both aspects highly time critical. Insufficient mixing or uneven acidic pH conditions can compromise viral clearance, product quality, and process continuity. Pionic® Spin solves these challenges through its smart design and advanced control mechanisms, ensuring consistent performance even under dynamic conditions.

The recirculation loop was engineered to ensure homogeneous acid-feed mixing and robust acidic pH adjustment. Turbulence is generated as the process stream circulates through the loop and becomes more intense upon entering the recirculation bag. The sudden expansion in the bag causes localized flow separation, which further enhances mixing efficiency. Potential pH fluctuations are mitigated by the volume-dependent increase in process inertia, which helps moderate rapid pH changes. This enables the pH control system to maintain the target pH setpoint with an accuracy of ±0.1 pH units and ensures correct pH measurement, representing an advantage over inline acid dosing via a T-junction.

Consistent homogeneous mixing is further achieved through dynamic, stepless weight-dependent mixing control, enabling precise and seamless adjustment of the mixing speed in the recirculation loop, homogenization bag, and neutralization bag. Real-time adjustments, even in response to minor deviations, ensure uniform, optimal mixing performance regardless of process scale or feed viscosity.

Acidic and neutral pH setpoints are precisely achieved and maintained by the pH control system, which combines traditional feedback with innovative disturbance control. The use of a process -specific titration curve eliminates the need for time-consuming and costly test runs to qualify the pH control system for maintaining both acidic and neutral pH setpoints during the cVI process.

Biobrain® software utilizes this titration data with the disturbance control signal to predict the required volume of acid or base. By integrating this predictive dosing with real-time feedback from both control loops, the software calculates the final acid or base demand, achieving an accuracy of ±0.1 pH in various scenarios.

With Pionic® Spin, Sartorius introduces an innovative solution for robust and reliable cVI through ICB. Intelligent design and innovative control mechanisms ensure process stability and resilience, even under varying process conditions and potential disturbances.

Pionic® Platform sets a new standard in the biomanufacturing of active pharmaceutical ingredients. Covering the downstream process from capture to UF | DF, individual Pionic® modules can replace traditional batch equipment up to level 3 ICB.[1,2] Designed to meet the growing industry shift towards ICB, Pionic® Platform enables a seamless transition from traditional batch processes, ensuring enhanced efficiency, flexibility, and scalability.

For more information, visit
sartorius.com/process-intensification

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