BIOTECH

Technical Regulatory Topic

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Automation and Control in Continuous Bioprocesses

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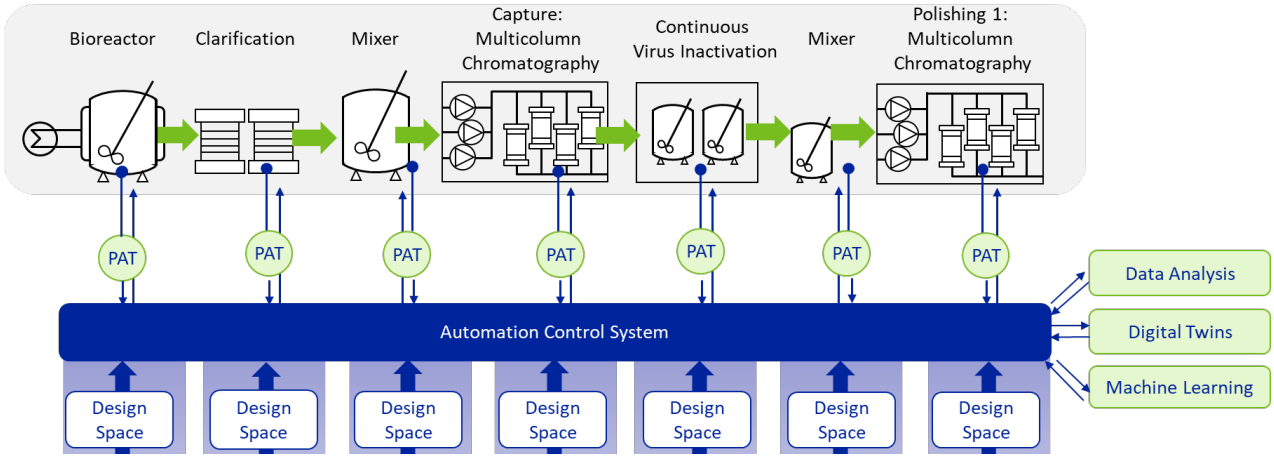
1 Control in Continuous Bioprocesses

Continuous bioprocessing is a key enabler for process intensification in the biopharmaceutical industry. Many platforms that are being developed or implemented today include one or several unit operations for continuous manufacture. Integrated bioprocesses are typically run over extended operating times of several days or weeks. Such platforms cannot be operated without an adequate level of automation to ensure continuous flow of the product from one-unit operation to the next. With the extended operation time and repetitive cycling of unit operations comes the need for long-term process consistency to assure that the product continuously meets quality specification. Figure 1 shows the conceptual setup of an automation control system: the system maintains the critical process parameters (CPPs) of all unit operations within their design space by analyzing and controlling the CPPs through—ideally—PAT-ready analytics and sensors. While it may seem that such automation concepts are a hurdle when implementing continuous bioprocessing, it provides a variety of opportunities for improved process understanding and control.

Figure 1.

Automation control system assuring that the process stays within the design space by assessing process information in real time through PAT. Advanced data analysis tools (e.g., multivariate data analysis), digital twins, and machine learning can thereby improve the responses from the control system.



1.1 Automation Strategies

A continuous platform connects multiple systems operating simultaneously, and therefore requires a robust automation platform for real-time process monitoring and decision making. The automated systems should work together in harmony to ensure that the product flows through the cascade of unit operations uninterrupted. Today, two automation principles are common in the biopharmaceutical industry:

- Distributed Control Systems (DCS)
- Programmable Logic Controllers (PLC) with a Supervisory Control and Data Acquisition (SCADA)

For continuous or integrated processes, these two automation principles come with challenges. In DCS, set point management and control as well as data collection are centralized, and all unit operation actions are coordinated. In processes that operate with a mixed selection of continuous unit operations this brings a harmonization advantage but a rather slow control speed. PLC/SCADA systems show a high speed of control because the control is typically localized on the unit operations, with only the setpoints and data acquisition being centralized. The downside of this approach is a more difficult harmonization and coordination between the individual unit operations.

Commonly in the industry both PLC/SCADA and DCS systems are combined as shown in proof-of-concept studies for integrated processes by Bayer◆ [1, 2], Merck◆ [3] and BiosanaPharma [4, 5]. Such hybrid automation and control platforms provide a high degree of process consistency by controlling the product flow rate. At the same time, automation presents an opportunity to reduce the risk of operator error, which is a main reason for batch rejection in both commercial and clinical manufacture [6].

The regulatory expectation towards such supervisory control systems is that they include both process control functionality and quality unit oversight [7]. Harmonizing control systems across different scales from process development to manufacturing enables a seamless technology transfer and data portability.

For integrated processes, a feed-forward flow control is seen as a bare minimum to control a process. It is aspired to engender more advanced control systems that include feedback from sensor readings within the PAT strategy , and adapt operating parameters to the fluid quality throughout the production, see Figure 1. Alarms and control measures assure that the system operates within predefined limits according to its design space. Automatic responses in case of process shifts can include for example, automated pauses to temporarily interrupt sections of the process, and automatically bring intermediate product solutions to safe condition, for instance by adjusting buffer conditions, or to divert product as shown in Figure 3.

1.2 Opportunities for PAT

The PAT approach is designed as a process control strategy based on real-time measurement of CPPs that correlate with critical quality attributes (CQAs). Its adoption is actively encouraged by regulatory authorities such as the US Federal Drug Administration (FDA). Dynamic control of CPPs has been commonly implemented in upstream processing where for example pH, dissolved gasses, temperature, or foam level is monitored and controlled online. In downstream processing, the dynamically controlled CPPs such as conductivity, pressure, or pH are in the minority, and a vast majority of the CPPs rely on a more static control. Additionally, typical quality attributes in Downstream Processing (DSP) such as product purity, charge variants, or information on impurities (DNA, endotoxins, host cell proteins, bioburden) can often not be detected directly. The current lack of sensors with a direct link to quality attributes has been described and recognized as a gap in biologics manufacture, especially for continuous processing [8, 9, 10]. Some continuous DSP unit operations, however, have opened a possibility to implement dynamic control strategies and advances in PAT implementation.

PAT that has been enabled through continuous design principles can be found in multicolumn chromatography. A dynamically controlled inline signal of the protein titer can be used to measure the load capacity in the chromatography column. This assures that each column of the multicolumn chromatography is loaded to the target capacity independent of cycle-to-cycle capacity decays or titer variability. This strategy is applied in the Periodic Countercurrent Chromatography (PCC) system of Cytiva◆ [11]. The technology implements Ultraviolet (UV) sensors both upstream and downstream of the chromatography column to detect protein breakthrough in real-time and react accordingly.

Such technologies are one step towards a holistic PAT strategy for an entire manufacturing platform. With more CPPs controlled based on process information more advanced process controls strategies such as model predictive control, machine learning, or artificial intelligence become an opportunity. Looking further into the future, real time release testing may become a vision as it is encouraged by both the FDA and European Medicines Agency (EMA) for continuous small molecule processes today [7, 12].

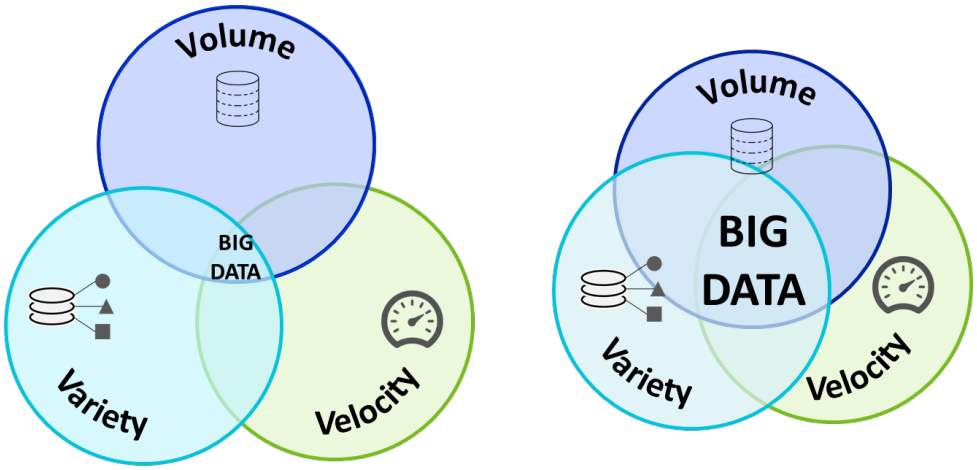
1.3 The Data Analysis Challenge

The data that is being produced during manufacture but also in process development experimentation consists of a larger volume compared to batch processing. Due to the extended operating times but also the repetitive, cyclic nature of many of the unit operations, several million data points can result from one manufacturing process. This requires an effective way to collect the data, process the information, and enable timely decision making. This challenge is commonly referred to as 'Big Data' which combines the three 'V's: 1) high-volume, 2) high-velocity, and 3) high-variety of information [13], and is conceptually shown in Figure 2.

In process intensification or continuous processing, it is not only the volume of data but also its velocity and variety that increases. With multiple unit operations connected in one DCS or PLC/SCADA, each carrying multiple sensors and instruments that produce data, the volume of data increases significantly. Additionally, the data sources can be very diverse since multiple different unit operations are operated in parallel, and offline data points may need to be correlated to specific events within that cascade. Further data variety is added by more complex analyzers such as Raman or Near Infrared Spectroscopy (NIR), or unstructured data for raw material or consumable traceability. The third aspect, velocity, describes the rate at which data is generated and requires processing. In continuous manufacture, there is little to no hold time of product between unit operations, and the time windows for decision making are much shorter. Process data therefore needs to be processed fast for rapid decisions.

Figure 2.

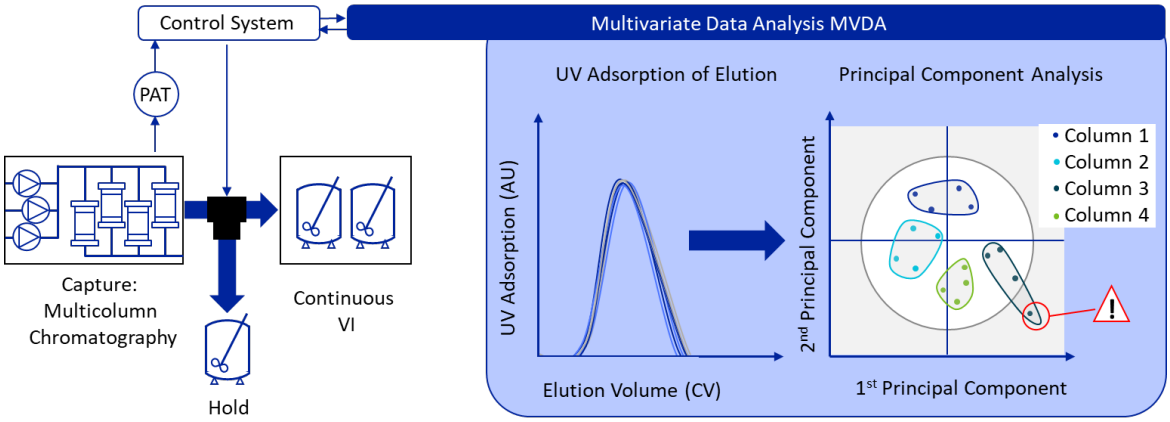
'Big Data' can be defined as the overlap of high-volume, high-velocity, and high-variety data. In continuous processing the 'Big Data' challenge increases because each of the three 'V's increases compared to batch operation.



While 'Big Data' may be a challenge, it also comes with numerous opportunities for advanced analysis and batch review. Multivariate data analysis (MVDA) is seen as a powerful tool for PAT and Quality by Design (QbD), and is particularly meaningful where multiple cycles of the same operation are performed, and a large amount of data is available for in-depth analysis [10]. MVDA provides more insight in the structure of the dataset and reveals even the smallest differences between data points. It has been applied mostly to upstream processing but has shown to also be an effective means for process control in downstream unit operations [10]. The example in Figure 3 shows how Principal Component Analysis (PCA), a form of MVDA, can evaluate even the smallest column-to-column and cycle-to-cycle variations in a multicolumn chromatography process. A trend can be recognized by MVDA before it is visible through traditional methods, and ideally even before it compromises product quality. Corrective actions can be taken before trends from upcoming column failure, or process variations become problematic. With the large amounts of data generated by the long-term operation or cyclic behavior of unit operations, MVDA can help manufacturers provide evidence of process control [14]. In addition, the PCA's ability to highlight process deviations aligns well with the approach of batch review-by-exception. Tools from the MVDA family hold the potential to use the large amount of data for a faster, more accurate, and robust data review, and hence batch review.

Figure 3.

Multivariate data analysis (MVDA) applied to 4 cycles of a 4-column multicolumn chromatography process to evaluate if UV adsorption values of elution peaks are within the design space. The example shows one elution of column 3 trending towards a potential out-of-specification. The control system can react in real-time and divert the eluted product to a hold container instead of forward processing it in the virus inactivation (VI) step.



2 Conclusion

The impact of 'Industry 4.0' becomes visible in continuous bioprocesses, and rapidly emerging opportunities in the digital era are pushing and supporting the implementation of intensified manufacturing concepts. Automation and control of integrated unit operations come with additional requirements. Today's common combination of DCS and PLC/SCADA has been successfully implemented in continuous processes as well. Implementing a seamless end-to-end PAT strategy over the entire platform is not yet a reality due to a lack of robust single-use on-line sensors. However, some continuous DSP unit operations have opened a possibility to implement dynamic control strategies and advance the PAT implementation. Intensified processes can generate the 'Big Data' problem because of the shear mass, variety, and velocity of the collected and processed data but, if managed well, opens the door to tools like model predictive control, machine learning, or artificial intelligence. Intensified platforms are aligned with 'Industry 4.0' and can benefit significantly from the transformations and progress associated with the digital maturation.

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