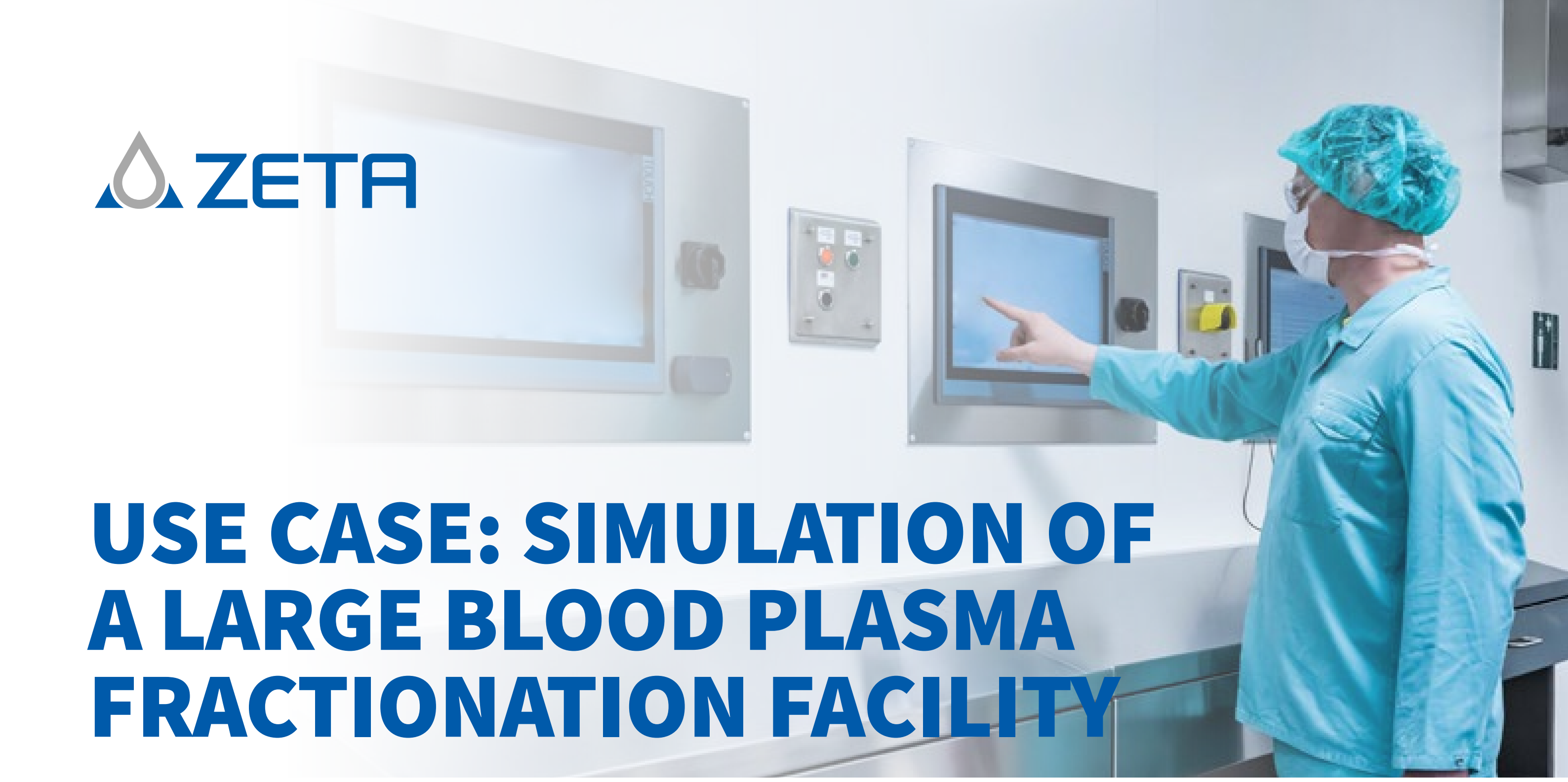


USE CASE: SIMULATION OF A LARGE BLOOD PLASMA FRACTIONATION FACILITY

This use case presents a simulation-based approach for analyzing capacity limits and identifying bottlenecks in a blood plasma fractionation facility. The study involved a capacity expansion of a production line, and a product changeover in three further production lines, requiring the development of new buffer handling strategies and optimizing measures. The modular and flexible setup of the simulation allowed for quick investigation of different scenarios and identification of specific measures to resolve bottlenecks and eliminate critical delays in the processes.

Facility description and challenges

The analyzed facility for blood plasma fractionation consists of four production lines (A, B, C, and D), on which different products are produced, with a fraction of the product of the previous line serving as the input material for the next line. The required buffers are produced in prep tanks and stored in corresponding hold tanks.

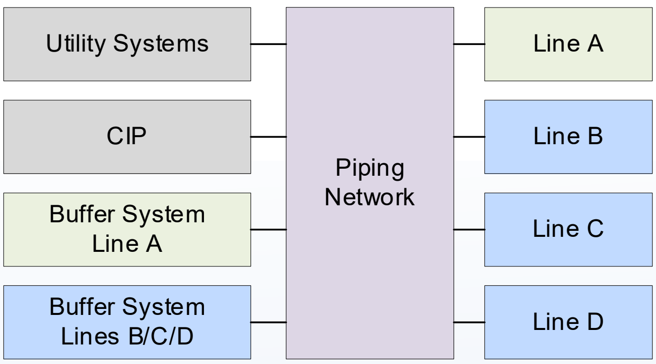


Figure 1: Facility system overview.

The buffer handling system for Line A is separate from the one for lines B/C/D. The concept for cleaning in place (CIP) includes CIP nodes, which means that all media for CIP is taken directly from the respective loops. The utility supply consists of WFI, caustic, and ethanol systems. The system is characterized by a complex piping network with shared pipelines and CIP nodes, and with shared equipment on a multi-line production.

Aim of the simulation

A capacity expansion of all production lines, as well as an upcoming product changeover on Lines B/C/D was planned. To analyze capacity limits of the highly complex facility's lines and supply systems, simulation was applied. The objective was to develop a suitable buffer handling concept and optimize it accordingly. To do so, bottlenecks were identified, and debottlenecking measures were derived, tested in the simulation, and optimized.

Approach

To set up the model, ZETA applied its modular simulation architecture. All production processes on the four lines were modeled in detail, on the basis of information derived from operation management, manufacturing instructions, and time measurements and observations at the real plant. In addition to the production processes at the core of the simulation architecture, all relevant support-systems were structured in layers. Those included buffer handling systems, CIP, utility systems and piping. Such a modular approach allows for fast and accurate implementation of different scenarios for testing, optimization, and future extension of the model.

New buffer handling strategy for Line A

Line A involves running a staggered chromatography process across three columns. The intention was to double the column volume from 100 L at 14 batches per week (Case A) to 200 L at 11 batches per week (Case B). The chromatography process requires eight different buffers. One buffer prep tank and eight buffer storage tanks,distributed into two areas, buffers A to C and buffers D to H, are used. The buffers are conveyed from the storage tanks over transfer panels to the corresponding chromatography column via a distribution matrix.

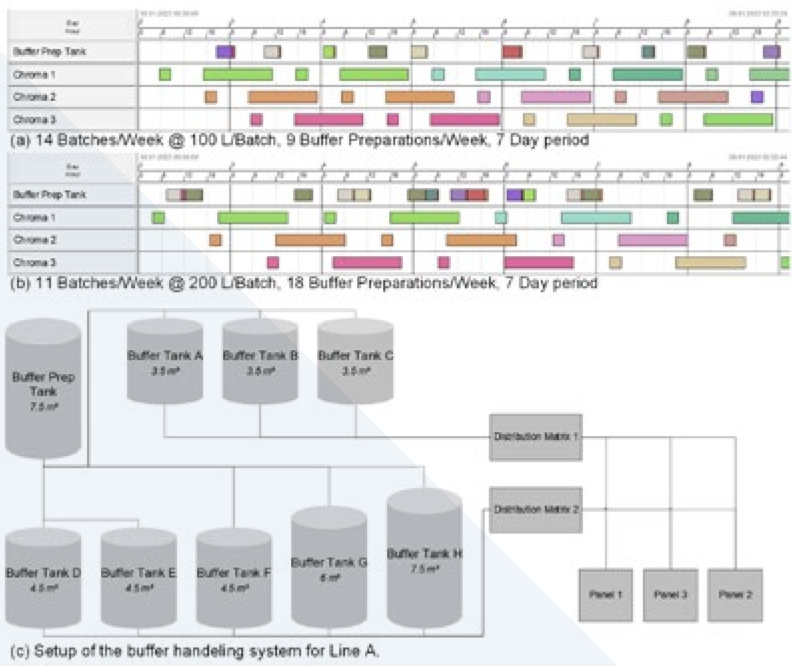


Figure 2: Buffer handling system (c) of line A prior (a) to and after the capacity extension (b).

An increase in production capacity requires a higher amount of buffers to be supplied. Due to the mechanical setup of this production line and limited availability of time windows in the production process, the timing buffer preparations is especially challenging. To handle the complexity of the buffer preparation system, a mathematical model was applied. Several strategies were discovered to be functioning, however, all of them would lead to increased buffer loss and tight time windows for the preparations. Therefore, it was concluded that by this approach very little room for errors is allowed and no feasible result could be obtained for the production process.

Consequently, a follow-up project was started in cooperation with the customer: Several scenarios featuring minor mechanical adaptations were evaluated by simulations, and analyzed in terms of flexibility, OPEX, process risk, and space requirements. Thanks to the modular and flexible structure of the simulation, these scenarios could be simulated and analyzed quickly. They included measures such as tank reassignments, one new larger storage tank, the use of buffer concentrates and in-line dilution (ILD) skids, as well as slight mechanical adjustments of the transfer piping network.

Debottlenecking of Lines B/C/D

On Lines B/C/D, a product change and capacity increase were planned. The new processes largely resembled the existing ones but should differ in terms of process times, utility- and buffer requirements. While in the original process not an issue, three process units (F01, F02 and F03) were identified as bottlenecks, as their occupancy rate nearly amounted to almost 100% in the new production scenario with capacity expansion. Even small process deviations or disruptions, such as valve failures or equipment downtimes, would have a significant impact on subsequent batches.

With the help of simulations and experienced process engineers, specific measures were identified to reduce overall utilization of these units. One measure was to reduce the duration of a pre-cleaning step from 2.5 hours to 1 hour, by providing higher WFI amounts. As recorded in the simulation, this was technically feasible, as sufficient loop capacity is given at the respective time.

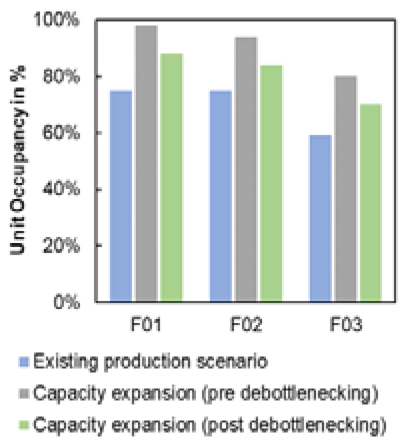


Figure 3: Unit occupation rate pre and post debottlenecking.

Optimization of buffer handling strategy of Lines B/C/D

The existing buffer system has to provide other buffers in different quantities for the new processes.

In this new production scenario, the buffer prep tank becomes a bottleneck. Additionally, a higher amount of buffer per batch is required. This means that, keeping the buffer storage tank at the existing size, a higher frequency of buffer preparations (about 14 buffer preparations per week instead of about four) is required to reach the higher production capacity.

To avoid overlaps that result in waiting times, several scenarios for the buffer preparation strategy were developed and tested in the simulation. This allowed to develop a robust and easy-to-execute strategy, mitigating the bottleneck. Figure 4 shows the allocation of the buffer prep tank over the same timeframe for the current and the new processes.

Analysis of CIP system

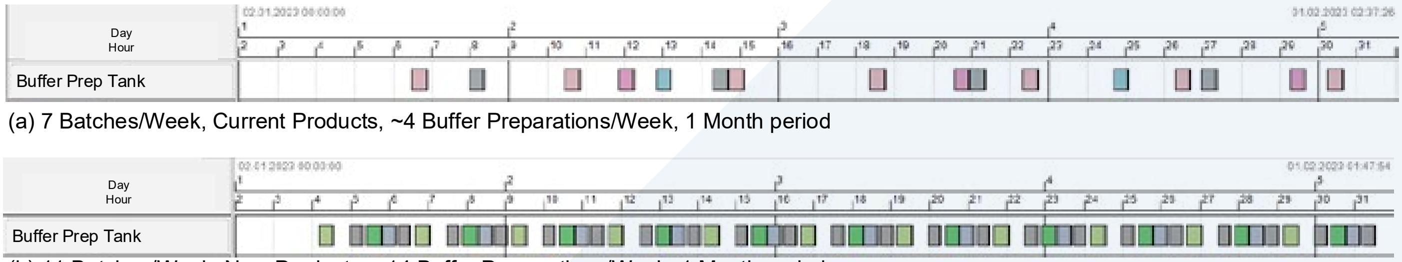
A further request of the customer's was the evaluation of the impact the product change and the capacity increase would have on the CIP system. In the described plant, the CIP system is realized via CIP-nodes and the CIP media (WFI, NaOH) come directly from the corresponding supply loops. When a unit is cleaned in-place, a CIP pre-rinse node and - depending on the piping configuration - one or more CIP post-rinse nodes are occupied for the entire duration of the CIP cleaning. CIP nodes are assigned to several units, which can cause timing conflicts. A detailed analysis was therefore carried out, to identify all possible conflicts.

Furthermore, a cause-effect analysis was conducted to observe the effects of time variations in the CIP process. The obtained information was then used to derive tangible measures for troubleshooting if these scenarios were to occur in real production.

Adjustment of WFI-system sanitization strategy

The sanitization of the WFI system was identified as a bottleneck of the plant in its the new operating mode. During two hours of sanitization, WFI is not available for other process operations. The existing operation comprises regular time periods without WFI usage in the process. In the new operation, however, WFI is almost constantly needed, and in turn sanitization is causing delays in the process.

Simulations helped to detect the problem early, allowing measures to be developed. Critical delays could be eliminated entirely by specific changes to the sanitation process within its validation boundaries.



(a) 7 Batches/Week, Current Products, ~4 Buffer Preparations/Week, 1 Month period

(b) 11 Batches/Week, New Products, ~14 Buffer Preparations/Week, 1 Month period

Figure 4: Allocation of the buffer prep tank

Summary and outlook

This use case shows that ZETA's application of production simulation in this project provided significant value for the customer, as major bottlenecks in various systems of the complex production facility were identified prior to project execution. Tangible measures for resolving bottlenecks and other issues that might occur were derived and tested under different scenarios in the simulation. These studies serve as a solid basis for the following project phases. The final, optimized process GANTT-chart is visualized in figure 5. ZETA's modular simulation architecture will allow this model to continue to provide significant value over the entire life cycle of the facility.

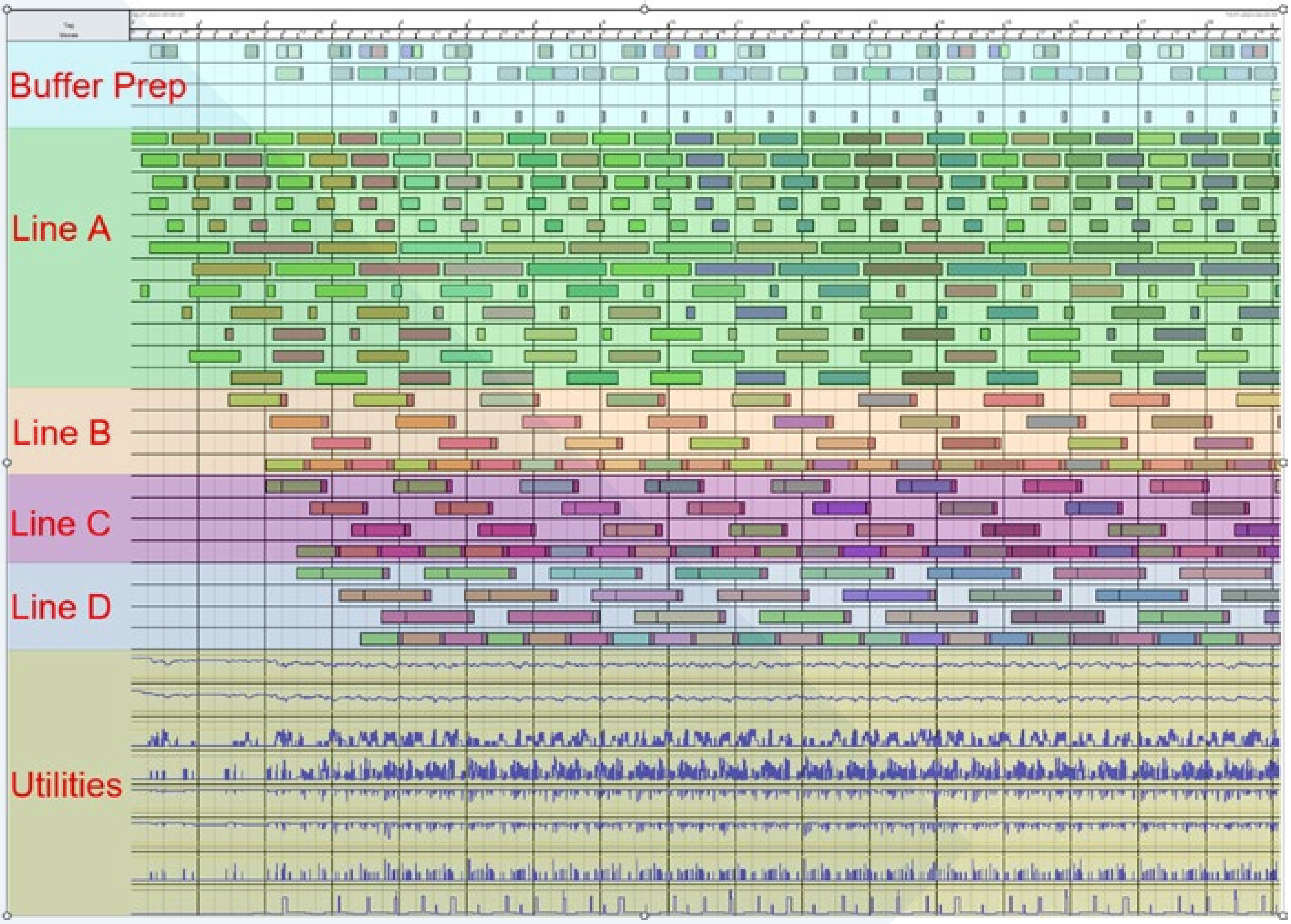


Figure 5: Final process GANTT-chart for the planned capacity extension and product changeover.

CONTACT

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ABOUT ZETA

As a globally operating end-to-end solution provider for the biopharma industry, ZETA specializes in the design, construction, automation, and qualification of customer-specific systems for aseptic production processes. ZETA offers comprehensive solutions and services along the whole pathway of active substance development and manufacturing.

As EPCM contractor, ZETA manages major, high-complexity pharma projects and specifically reduces interfaces—from the planning and construction of the process system through the cleanroom design up to the technical building infrastructure. This design-build approach accelerates the project execution time by up to 50% and leads to creation of value earlier in the customer's capex projects. In addition, ZETA drives digital innovations, and develops comprehensive decarbonization strategies.