Success Story: Optimizing Protein Precipitation and Separation through Hybrid Modeling Approaches

A Global Challenge

Fractional protein precipitation from blood plasma is a critical step in Takeda's biopharmaceutical manufacturing. Achieving high product quality and reliable protein separation is, however, far from trivial. Numerous interdependent factors - such as mixing dynamics, shear rates, and local concentration gradients - affect not only the efficiency of separation but also the structural integrity of the precipitated proteins. Takeda Manufacturing Austria AG approached this challenge with a clear ambition: to identify an optimal tank, stirrer design in combination with an optimized stirring process (e.g. stirring rates) that could be implemented consistently across its production sites worldwide for each process step. The key requirements were robust performance and preservation of protein quality.

How RCPE's Twin4Pharma Advances Tank Design through Hybrid Modeling

As part of the *Twin4Pharma* module, RCPE GmbH and the Austrian Start-up Simvantage GmbH contribute through the creation of advanced process models that combine **first-principle simulations** with **data-driven methods**. This hybrid approach enables us to explore tank and stirrer design behavior *in silico* and to establish correlations between reactor and stirrer design, precipitation strategy, and critical product outcomes such as separability, filterability and precipitation specificity.

From Reactor Characterization to Process Optimization

Our investigations began with a systematic characterization of one reference reactor of one defined process step. By determining its steady-state conditions, we created a reliable baseline for subsequent studies. We then extended the analysis to transient regimes, gaining insights into how geometric variations and operational changes affect mixing performance.

Key steps included:

- **Mixing time determination** at varying impeller speeds, serving as reference metrics for homogeneity and providing valuable input for scale-up considerations.
- **Comparative evaluation of feeding strategies**. The results indicated substantial improvements: mixing times could be reduced by up to 35%, while mitigating overconcentration peaks that would otherwise compromise protein quality and stability.

First Success: Validating the Approach

An early and important achievement of the project was the validation of our modeling strategy as a tool to compare different tank geometries and precipitation-agent feeding methods. The simulations revealed that the **manner of precipitant addition is just as critical as reactor design** itself. Local overdosing of the precipitating agent - if uncontrolled - leads to unwanted precipitation and potential protein denaturation. Our hybrid approach provided a clear preference

for optimized distribution methods, enabling significantly improved process consistency and product quality.

Looking Ahead

The ongoing project now moves toward the next milestone: translating these validated insights into the design of an **optimal tank configuration** for Takeda´s plasma protein precipitation. In addition, equivalence mapping between different reactors will ensure that the optimized design can be reliably scaled and transferred across global production facilities. This step is crucial, as reproducibility across sites guarantees not only efficiency but also patient safety.

Impact and Outlook

Through the combined application of rigorous physical principles and modern data-driven analytics, the project lays a solid foundation for Takeda´s **next-generation plasma fractionation processes**. The first results clearly demonstrate that challenges in precipitation homogeneity and protein quality can be addressed systematically, and that improved designs are within reach. The long-term impact will be to enable more reliable, efficient, and scalable processes across the global production network, thereby strengthening both quality assurance and competitiveness.

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