Applications of Process Modeling and Optimization in Biopharmaceutical Manufacturing

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With the increasing global market demand, prohibitive drug cost, and biosimilars competition, the biopharmaceutical industry is under pressure to speed up the development and manufacturing of biological products. To increase biologics production while maintaining product quality, the industry attempts to 1) improve the processes through intensification and optimization, and 2) explore new process designs. This shift increases the complexity of bioprocess and also the number of process variables to be monitored. Moreover, the Quality-by-Design (QbD) initiative introduced by FDA to take product quality into account during the process design, is driving the biopharma industry to acquire deeper process insights. With the increasing demand for process understandings and the pressure in cost reduction, the industry is turning to *in silico* solutions to assist with such a transition. Given the industrial trend, this dissertation aims to apply process systems engineering (PSE) tools to empower the *in silico* development of biopharmaceutical manufacturing processes.

The first part of the thesis, as presented in Chapters 2-4, focuses on the applications of PSE tools on individual unit operations, specifically various chromatography units, to support process characterization and optimization. In Chapter 2, a surrogate-based feasibility analysis method is proposed to identify the design space of continuous Protein A chromatography, aiming to strike a balance between computational complexity and model prediction accuracy. Machine learning-based optimization framework is introduced in Chapter 3 to address the nonconvex and nonlinear constrained optimization challenges encountered in biopharmaceutical separation. This framework is applied to a case study involving the separation of a ternary protein mixture using ion-exchange chromatography. The focus of Chapter 4 is to develop hybrid models with enhanced model

predictability to describe the unclear and complex binding behavior within the hydrophobic interaction chromatography. The aim is to reduce the investment effort required for developing mechanistic model while extracting the missing relationships that cannot be captured by the mechanistic model.

Considering the trend in transitioning from batch to continuous processes, the second part of the thesis focuses on conducting proof-of-concept study to evaluate the feasibility of transitioning from batch to continuous biomanufacturing mode through the establishment of *in silico* platform, as presented in Chapter 5.

The applications of PSE tools in the biopharmaceutical processes, specifically through process modeling and system analysis, have demonstrated significant potential in enhancing process understanding and facilitating process development / improvement. The proposed methodologies and frameworks proposed in this dissertation can provide further insights into the cost-effective development and manufacturing of high-quality biological drugs, promoting further investigation and implementation of *in silico* technology in biopharmaceutical industry.