Thesis Title: Systems Engineering for Biopharmaceutical Manufacturing Processes with Phase Transitions
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Date: July 31, 2025
Location: 56-154
Time: 10:00AM-12:00PM (ET)
Zoom link: https://mit.zoom.us/j/93525181898

Abstract:
The biopharmaceutical industry has witnessed substantial growth over the past decade. The rise of various biotherapeutics, such as monoclonal antibodies, cell and gene therapy, and mRNA vaccines, has played a crucial role in advancing global health, offering targeted and effective treatments for an array of diseases. Nevertheless, the current biopharmaceutical manufacturing is facing several challenges associated with production scalability, operational flexibility, and quality control. For example, many biopharmaceutical processes are still operated in batch mode, unlike major industrial sectors that have already adopted continuous manufacturing. As such, significant efforts have been recently dedicated to the development and integration of advanced manufacturing technology for biopharmaceutical processes.

This thesis presents a set of novel computational tools and methods across process systems engineering (PSE) domains developed for biopharmaceutical manufacturing. Several PSE applications are discussed and demonstrated, including process modeling, monitoring and state estimation, model-based control and optimization, and uncertainty quantification. Two important biopharmaceutical processes that involve phase transitions are studied, namely (1) lyophilization and (2) cell thawing, serving as the two main parts of this thesis.

This thesis defense will primarily focus on the first part, namely lyophilization. Lyophilization (also known as freeze drying) is a low-temperature, low-pressure dehydration process that has been widely used in the (bio)pharmaceutical industry to improve the stability of various drug products, including its recent application to mRNA vaccines for COVID-19. In this talk, several PSE techniques for lyophilization will be presented. First, I will describe a novel mechanistic model for lyophilization, specifically the state-of-the-art continuous lyophilization technology via suspended vials. The validated models can predict the evolution of critical process parameters and critical quality attributes, including the product temperature, ice/water fraction, sublimation front position, and residual moisture (bound water), throughout the entire lyophilization cycle. Second, I will showcase a state observer that estimates the residual moisture by using temperature measurement as an input. This state observer allows for real-time tracking of the residual moisture, which is typically present in trace amounts and difficult to measure online. Third, I will discuss a highly efficient framework for incorporating the probabilistic uncertainty into the lyophilization model via polynomial chaos theory (PCT). The PCT-based lyophilization model is applied for fast uncertainty quantification and stochastic optimization of the lyophilization process. Finally, I will describe a new, efficient optimal control algorithm via reformulation and

simulation of hybrid discrete/continuous mixed-index differential-algebraic equations (DAEs). The proposed algorithm is employed for finding the optimal control policies for lyophilization under different conditions, which is shown to be several orders of magnitude faster than the traditional methods while maintaining similar/better accuracy. With all the tools and methods developed in this thesis, we provide a complete PSE framework and case studies for advanced manufacturing of biopharmaceutical processes with phase transitions.