Continuous Biopharmaceutical Manufacturing
Modeling, Control, and Process Intensification

by

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ABSTRACT

Compared to traditional batch manufacturing routes, continuous biopharmaceutical manufacturing is a fast-approaching paradigm with the potential to save time, money, and lives. Achieving these gains, however, requires a suite of predictive, diagnostic, and corrective tools which are formalized in the Process Systems Engineering (PSE) field. Throughout this thesis, I focus on understanding and applying these PSE tools analytically and numerically to a variety of continuous upstream and downstream unit operations in biomanufacturing applications. My efforts can be summarized in three complementary aims that mirror the thesis title:

1. *Modeling.* Answering questions of process model utility and process observability through model synthesis, selection, and identification—the tasks most tightly linked to observation and experimentation. These tools require real-time and/or big data processing coupled with fast numerical simulations of dynamic models. Dynamic models of concern here are for: (a) intrinsically distributed operations, i.e., which for the particle-laden, multi-phase systems appearing in this thesis are described by population balance models (PBMs); and for (b) strongly timescale-separated operations, i.e., which are described by differential algebraic equations (DAEs). Model-order reductions by engineering assumptions are used to yield useful approximate models. Selected works include the unstructured, non-segregated modeling of continuous viral vaccine manufacturing, and the integro-partial differential algebraic equation (IPDAE) nucleation-growth modeling of morphologically-varied, speciation-sensitive co-crystallizing pharmaceuticals;

2. *Control.* Answering questions of process controllability through closed-loop (i.e., controlled process) synthesis. Here I applied a variety of optimization-based controls methods (e.g., dynamic optimization, nonlinear model predictive control, stochastic nonlinear model predictive control) for optimizing objectives relevant to biomanufacturing, e.g., production process costs and critical quality attributes (CQAs), on the large-scale integro-partial differential equation (IPDE)-constrained problems that particulate biopharmaceutical processes actually pose. Selected works include oscillatory yeast cell manufacturing optimization and stochastic model predictive control of a dynamic tubular precipitator;

3. *Process intensification.* Answering questions of process intensification. These questions consider continuous operation, staged reactor design, and scale-down high-throughput experimentation, all of which may return more product, more information, or both, per unit

of material, or time, or capital than the batch-mode practices they replace. The inquiry is supported by robust open-loop (i.e., uncontrolled process) analysis and closed-loop synthesis. These techniques involve using current and previous experimental studies to perform parameter estimation, uncertainty quantification, and identifiability studies on proposed models, which make each intensification claim falsifiable. Selected works include the demonstration of viral vaccine production in two-stage stirred tank reactors and scale-down, high-throughput optical imaging studies and kinetics estimation of the co-crystallizing pharmaceuticals.

Altogether my focus points have revealed some larger gaps holding back current biomanufacturing practice. These gaps include, but are not limited to: real-time observability limitations on feature distributions in particle-laden systems (e.g., cell morphologies or crystal size distributions); the lack of identifiable higher-fidelity process models to describe these processes to perform soft-sensing fusion with the data they generate; and availability of performant numerical algorithms to simulate and act on these capital-intense processes using cheap digital twins. *With so many academic and non-academic details, the guiding principle is to help practically close a portion of these gaps in the biopharmaceuticals manufacturing sector in current and future work.*

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