Systems Engineering for Biomanufacturing

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Biologics are an important class of drugs that have seen rapid growth in recent years. However, complexities in production and characterization result in large-scale centralized production and cold chain distribution being the primary logistical paradigm. The large upfront costs limit the ability to address small patient population needs of precision medicine and orphan drugs. The cold chain requirements also limits therapeutic potential in the developing world, crisis scenarios in the developed world, and requires stockpiling for pandemic response.

To address these currently unmet needs, this thesis develops the Integrated Scalable Cyto-Technology (InSCyT), a fully automated and integrated biomanufacturing platform. It comprises of a continuous perfusion bioreactor cultivating the host Pichia pastoris, a continuous pH adjustment unit, three chromatography columns, and a tangential flow ultrafiltration unit. It enables hands-free production of hundreds to thousands of doses of clinical quality biologics in final dosage form in about three days. We demonstrate the production of human growth hormone, interferon α-2b, and granulocyte colony-stimulating factor and show purity and potency comparable to currently marketed products.

The thesis then addresses systems engineering problems within InSCyT. On-demand buffer production requires fast and accurate control of both conductivity and pH. We model a buffer production unit and improve pH control performance through the use of reaction-invariant model-based nonlinear control and maximum a posteriori adaptation techniques to address system nonlinearity and parametric model uncertainty respectively. We validate the in silico results with experimental testing in a single-use disposable prototype. We also model the genomic stability of Pichia pastoris through copy number variability. This framework allows for the distillation of existing literature data into a single strain and product specific rate constant controlling copy loss. These models then allow us to evaluate antibiotic selection and continuous seeding as methods to ensure consistent productivity and quality over extended production periods. Lastly, we develop and experimentally demonstrate an in-reactor hollow fiber cell separator for perfusion operation in single-use disposable reactors. Improvements to the design are suggested through the use of computational fluid dynamics (CFD) simulations coupled with a fouling model for geometry optimization.

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