OPTIMIZATION TECHNIQUES FOR PHARMACEUTICAL MANUFACTURING AND DESIGN SPACE ANALYSIS

In this dissertation, numerical analysis frameworks and software tools for digital design of process systems are developed. More specifically, these tools have been focused on digital design within the pharmaceutical manufacturing space. Batch processing represents the traditional and still predominant pathway to manufacture pharmaceuticals in both the drug substance and drug product spaces. Drug substance processes start with raw materials or precursors to produce an active pharmaceutical ingredient (API) through synthesis and purification. Drug product processes take this pure API in powder form, add excipients, and process the powder into consumer doses such as capsules or tablets.

Continuous manufacturing has allowed many other chemical industries to take advantage of real-time process management through process control, process optimization, and real-time detection of off-spec material. Also, the possibility to reduce total cleaning time of units and encourage green chemistry through solvent reduction or recycling make continuous manufacturing an attractive alternative to batch manufacturing. However, to fully understand and take advantage of real-time process management, digital tools are required, both as soft sensors during process control or during process design and optimization.

Since the shift from batch to continuous manufacturing will proceed in stages, processes will likely adopt both continuous and batch unit operations in the same process, which we will call *hybrid* pharmaceutical manufacturing routes. Even though these processes will soon become common in the industry, digital tools that address comparison of batch, hybrid, and continuous manufacturing routes in the pharmaceutical space are lacking. This is especially true when considering hybrid routes. For this reason, PharmaPy, an open-source tool for pharmaceutical process development, was created to address rapid in-silico design of hybrid pharmaceutical processes.

Throughout this work, the focus is on analyzing alternative operating modes within the drug substance manufacturing context. First, the mathematical models for PharmaPy's synthesis, crystallization, and filtration units are discussed. Then, the simulation capabilities of PharmaPy are highlighted, showcasing dynamic simulation of both fully continuous

and hybrid processes. However, the technical focus of the work as a whole is primarily on optimization techniques for pharmaceutical process design. Thus, many derivative-free optimization frameworks for simulation-optimization were constructed and utilized with PharmaPy performing simulations of pharmaceutical processes.

The timeline of work originally began with derivative-based methods to solve mixed-integer programs (MIP) for water network sampling and security, as well as nonlinear programs (NLPs) and some mixed-integer nonlinear programs (MINLPs) for design space and feasibility analysis. Therefore, a method for process design that combines both the ease of implementation from a process simulator (PharmaPy) with the computational performance of derivative-based optimization was implemented. Recent developments in Pyomo through the PyNumero package allow callbacks to an input-output or black-box model while using IPOPT as a derivative-based solver through the cyipopt interface. Using this approach, it was found that using a PharmaPy simulation as a black box within a derivative-based solver resulted in quicker solve times when compared with traditional derivative-free optimization strategies, and offers a much quicker implementation strategy than using a simultaneous equation-oriented algebraic definition of the problem.

Also, uncertainty exists in virtually all process systems. Traditionally, uncertainty is analyzed through sampling approaches such as Monte Carlo simulation. These sampling approaches quickly become computational obstacles as problem scale increases. In the 1980s, chemical plant design under uncertainty through *flexibility analysis* became an option for explicitly considering model uncertainty using mathematical programming. However, such formulations provide computational obstacles of their own as most process models produce challenging MINLPs under the flexibility analysis framework.

Specifically when considering pharmaceutical processes, recent initiatives by the FDA have peaked interest in flexibility analysis because of the so called *design space*. The design space is the region for which critical quality attributes (CQAs) may be guaranteed over a set of interactions between the inputs and process parameters. Since uncertainty is intrinsic to such operations, industry is interested in guaranteeing that CQAs hold with a set confidence level over a given operating region. In this work, the *probabilistic design space* defined by these levels of confidence is presented to address the computational advantages

of using a fully model-based flexibility analysis framework instead of a Monte Carlo sampling approach. From the results, it is seen that using the flexibility analysis framework decreased design space identification time by more than two orders of magnitude.

Given implementation difficulty with new digital tools for both students and professionals, educational material was developed for PharmaPy and was presented as part of a pharmaceutical API process development course at Purdue. The students were surveyed afterward and many of the students found the framework to be approachable through the use of Jupyter notebooks, and would consider using PharmaPy and Python for pharmaceutical modeling and data analysis in the future, respectively.

Through software development and the development of numerical analysis frameworks, digital design of pharmaceutical processes has expanded and become more approachable. The incorporation of rigorous simulations under process uncertainty promotes the use of digital tools in regulatory filings and reduces unnecessary process development costs using model-based design. Examples of these improvements are evident through the development of PharmaPy, a simulation-optimization framework using PharmaPy, and flexibility analysis tools. These tools resulted in a computational benefit of 1 to 2 orders of magnitude when compared to methods used in practice and in some cases reduce the modeling time required to determine optimal operating conditions, or the design space of a pharmaceutical manufacturing process.