EFCE Excellence Award in Recognition of Outstanding PhD Thesis on CAPE

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PhD Thesis Title

Digitalizing Pharmaceutical Development and Manufacturing: Advanced Mathematical Modeling for Operation Design, Process Monitoring and Process Control

Summary

This Thesis is successful in presenting novel process systems engineering tools and applications for addressing critical challenges in pharmaceutical development and manufacturing. Novel models of pharmaceutical unit operations and algorithms are developed and used for (i) process design, (ii) operation design, (iii) process monitoring, and (iv) process control. Further, novel model-based tools are introduced for enabling the transition to end-to-end continuous manufacturing, more efficient than traditional batch pharmaceutical manufacturing. Overall, **10 first-authored peer-reviewed publications**[1–10] stemmed from this Thesis (6 journal articles and 4 contributions to proceedings of international conferences),

and **one co-authored book chapter**.[11] The peer-reviewed publications derived from the Thesis have collectively received **120**[†] **citations** as of December 2023 (Google Scholar). This citation record is even more impressive considering that it has been collected in about three years (first article published in July 2020). Further, Dr. Francesco Destro has been invited by MathWorks to give an invited lecture about his Thesis within the prestigious 2023 MATLAB Chemical Engineering Webinar Series, in April 2023.

The research related to the PhD Thesis has been conducted at the CAPE-Lab at University of Padova under the supervision of Prof. Massimiliano Barolo, and in collaboration with top-tier academic and industrial institutions. From September to December 2019, Dr. Francesco Destro was an invited Visiting PhD Student at Siemens Process Systems Engineering (London, United Kingdom), under the supervision of Prof. Constantinos C. Pantelides. From February to November 2020, and from January to March 2022, Dr. Destro was a Visiting PhD Student at Purdue University (West Lafayette, IN, United States of America; USA), advised by Prof. Zoltan K. Nagy, working on a project in collaboration with the United States Food & Drug Administration. Further, two of the journal articles related to the Thesis have been published in a collaboration with Eli Lilly & Company. Dr. Destro, currently a postdoctoral associate at the Massachusetts Institute of Technology (Cambridge, MA, USA), is collaborating with Takeda Pharmaceuticals (Cambridge, MA, USA), independently from his PhD and postodoctoral advisors, to implement in a plant of Takeda's a digital twin developed during his PhD(ContCarSim, see following sections).

The following sections summarize the problem addressed by the PhD Thesis, the state of the art before of the PhD research, and the key innovations and results of the Thesis.

Problem Addressed

Recently, the European Medicines Agency and the United States Food & Drug Administration have been registering an alarming number of drug shortages and recalls.[12] At the same

[†]citations to publications not related to the PhD Thesis have been omitted in the reported citation count

time, the cost (∼2B) and time (∼10 years) for bringing new pharmaceutical products to the market has increased dramatically.[9] In light of these events, there is a pressing need to enhance the efficiency of pharmaceutical development and manufacturing.

State of the art

The pharmaceutical industry has been responding to these issues through a modernization of development and manufacturing, under the support of the quality-by-design initiative from regulators.[13] A thorough overview of the state of modernization of pharmaceutical development and manufacturing is given in Chapter 1 of the Thesis. The following gaps were present in the state of the art before of the Thesis:

- advanced model-based monitoring techniques, such as state estimation, had never been applied for monitoring critical quality attributes in drug product manufacturing, despite the pivotal importance of quality attainment for pharmaceuticals;
- need for algorithms for hybrid modeling of pharmaceutical processes, to meet the quality-by-design mandate of building control strategies rooted in process understanding;
- pharmaceutical manufacturing was still heavily relying on batch implementations, although continuous processing can guarantee better efficiency, quality consistency, and controllability;
- model-based design and control of end-to-end continuous pharmaceutical manufacturing was limited by shortcomings in models for slurry filtration, washing, and drying;
- digital design and closed-loop control of pharmaceutical processes were poorly explored;
- few studies described the experimental validation of in silico results;
- lack of benchmark simulators for pharmaceutical processes, to test algorithms for computer-aided operation design, process control, and process monitoring.

Key innovations

The Thesis makes several steps forward in enhancing the efficiency of pharmaceutical development and manufacturing through studies on continuous pharmaceutical manufacturing, process monitoring, and model-based operation design and control. More specifically, the gaps outlined in the previous section are addressed:

- the first implementation of state estimation for monitoring the quality of pharmaceutical tablets in continuous solid dosage form manufacturing is demonstrated (Chapter 2 and related publications[3]). The state estimator is validated on data from a plant of an industrial collaborator (Eli Lilly & Company, USA);

- a novel hybrid modeling methodology for process monitoring is developed (Chapter 3 and related publications[1,2]). The proposed algorithm significantly outperforms the fault detection and diagnosis performance of state of the art algorithms, for both pharmaceutical processes and, more in general, for process systems;

- model-based tools and applications are developed to support the transition to continuous pharmaceutical manufacturing. The case studies discussed in the thesis involve continuous implementations of several unit operations of a pharmaceutical plant, such as continuous solid dosage form manufacturing, continuous purification, and continuous fluid drying;

- the first models for continuous integrated filtration, washing, and drying of pharmaceutical slurries are developed.[4] These unit operations are critical for connecting upstream and downstream pharmaceutical manufacturing into an end-to-end continuous framework, but they had been completely overlooked by the literature;

- the developed models for continuous slurry filtration, washing, and drying are used for demonstrating for the first time the digital design and the model-based control of a novel continuous carousel for active pharmaceutical ingredient purification (Chapters

4–5 and related publications[5–7,10]). One of the first implementation of closed-loop control of quality variables in pharmaceutical manufacturing is demonstrated, including model-based control;

- the models for continuous slurry filtration, washing, and drying are validated on a pilot-scale carousel for continuous active pharmaceutical ingredient purification;[4,8]

- a benchmark simulator of the carousel is developed: ContCarSim, continuous carousel simulator.[8] The simulator is a useful tool for the pharma community, for testing the digital design of continuous filtration-drying, but also for the control community, as a benchmark for testing novel control and monitoring algorithms. The simulator is available at: www.github.com/CryPTSys/ContCarSim.

A more detailed overview of the results and of the innovations introduced by the Thesis is given in the next section.

Results

An enhanced monitoring system for continuous manufacturing of pharmaceutical tablets

Pharmaceutical direct compression lines are made up of three main sections: feeding, mixing, and tableting. Active ingredients in powder form are first mixed with inactive ingredients, such as excipients and lubricants. Each ingredient is individually fed to the mixing section of the process through a separate feeder, which provides a continuous powder flow downstream. The powder mixture is then fed to a tablet press, where it is transformed into pharmaceutical tablets to be delivered to patients. Within the feeding-mixing sections of the process, it is crucial to mix the active ingredient with the inactive ingredients in accurate ratios, so that the final tablets contain the target content of active pharmaceutical ingredient. However, the composition of the powder mixture fed to the tablet press is oftentimes not directly

measured, but obtained as calculation from the mass flow delivered by each of the feeders supplying the blend ingredients upstream. Such estimation is very poor and cannot be used for proper quality monitoring, since it is numerically inferred from the time series of (very noisy) measurements of powder net weight in the hopper of the feeders. When the composition of the final tablet coming out from the direct compression line is eventually measured through high-performance liquid chromatography (HPLC), no more corrective actions are possible, and tablets that do not meet the target active ingredient content have to be discarded.

In Chapter 2 of the Dissertation, a novel approach is presented for monitoring powder feeding in continuous solid-dosage form manufacturing.[3] The monitoring system is based on a state estimator (moving horizon estimator), which effectively reconciles the mass measurements coming from loss-in-weight feeders with downstream measurements coming from a process analytical technology (PAT) instrument, and estimates the delivered powder mass flows by means of a model-based optimization strategy. The monitoring system exploits a detailed mathematical model of the process for state estimation purposes, allowing to develop control strategies rooted on enhanced process understanding. Successful validation is demonstrated with datasets collected on a direct compression line of an industrial collaborator (Eli Lilly & Company, Indianapolis, IN; USA). The results demonstrate for the first time the use of state estimation for identifying powder mixtures that are out of specification in the early sections of direct compression lines. The developed monitoring system allows to implement correcting actions for avoiding to discard any amount of precious active pharmaceutical ingredients.

A novel algorithm for hybrid data-driven/knowledge-driven process monitoring

A novel methodology for process monitoring, based on hybrid data-driven/knowledge-driven modeling, is introduced in Chapter 3 of the Dissertation and in the related peer-reviewed pub-

lications.[1,2] The developed approach merges traditional standalone data-driven and knowledge-driven process monitoring techniques in an innovative way, taking the advantages of both. In the proposed framework, real-time deterministic information about the process is first obtained in a knowledge-driven block from a state estimator in the form of estimated states, reconstructed measurements, and, possibly, estimated parameters. The information is then passed to a data-driven block, where it is exploited, in conjunction with the available process measurements, by a latent-variable model that accomplishes multivariate fault detection and diagnosis. The design of the two blocks is largely independent, which makes implementation of the proposed methodology easier. The hybrid methodology is tested on three case studies. In all case studies, the proposed hybrid monitoring system allowed for earlier fault detection than standard data-driven and knowledge-driven approaches taken in isolation, even when the state estimator did not perform entirely satisfactorily. In addition, using the hybrid approach significantly facilitated fault diagnosis. The very satisfactory fault detection performance of the hybrid approach derives from the fact that the estimated states provide a set of additional variables a fault can leave a footprint on. In most cases, these variables respond to the fault earlier than the measurements, causing an anticipated shift or break of the normal correlation structure of the data. One of the case studies for the novel algorithm was developed during a stay as Visiting PhD Student within the headquarters of Siemens Process Systems Engineering (SPSE; London, UK), advised by Prof. Constantinos C. Pantelides. The case study developed at SPSE focuses on a novel continuous segmented fluid bed dryer for pharmaceutical applications. The groundbreaking results and the industrial application showcase the high impact of the developed algorithm for hybrid process monitoring.

Continuous filtration-drying of pharmaceuticals: mechanistic modeling and design space description

Chapter 4 and the related peer-reviewed publications[4,6] present the first mechanistic model for a novel carousel for continuous filtration-drying of crystallization slurries. The model is

used for determining the probabilistic design space of the unit. The continuous carousel, developed and manufactured by Alconbury Weston Ltd (Stoke-on-Trent, UK), is one of the few technologies for continuous integrated filtration and drying of crystallization slurries. This process is particularly suitable for purifying crystals of active pharmaceutical ingredients from reaction solvents. Filtration and drying of crystallization slurries are pivotal unit operations for connecting the drug substance and drug product manufacturing sections of a pharmaceutical manufacturing process into an end-to-end continuous integrated system. However, prior literature contributions on continuous processing focus on other unit operations, such as reacting systems and crystallization. The modeling and experimental activities presented in the Thesis tackle this gap. The model is developed by assembling together independent filtration, deliquoring, washing and drying modeling components. A case study is developed on the digital design of paracetamol isolation from a crystallization slurry. After successfully calibrating the model with filtration and drying experiments, the probabilistic design space is identified. Model uncertainty is considered through Monte Carlo simulations, and the maximum throughput that can be processed in the carousel with acceptable probability of meeting the product quality specifications is also evaluated. The proposed approach to the digital design of continuous integrated crystals isolation is the first of its kind, and it represents a step forward towards end-to-end continuous pharmaceutical manufacturing.

Continuous filtration-drying of pharmaceuticals: quality-by-control through a novel digital twin

Following a life cycle approach to process modeling, the model used for designing the carousel operation in Chapter 4 is then further developed in Chapter 5 into ContCarSim, a benchmark simulator for testing advanced control strategies (www.github.com/CryPTSys/ContCarSim).[10] The simulator is a useful tool for both the pharma community, for digital design of continuous filtration-drying, and for the control community, as a benchmark for testing novel control and monitoring algorithms. ContCarSim is based on partial differential equations mechanistic

models, validated with data from a pilot scale carousel installed in Prof. Nagy's laboratory at Purdue University. A set of variability sources are implemented, mimicking the behavior of real-life carousels. The simulator can be operated in normal operating conditions or in additional disturbance scenarios, featuring the occurrence of abnormal events, such as a change in the concentration in the feed slurry, or a change in the specific resistance of the cakes formed in the carousel. A series of quality-by-design and quality-by-control challenges that can be addressed using the simulator are also proposed for benchmarking monitoring and control algorithms. In Chapter 5 of the Thesis, an innovative closed-loop control strategy is also proposed for the carousel for the first time. The proposed control strategy includes advanced model-based routines, such as state estimation and real time optimization. The conceived control system is tested on ContCarSim, under a set of disturbances known to affect the unit operation (e.g., filter mesh fouling), and it demonstrates superior control performance compared to traditional quality-by-design control strategies, based on open-loop quality control within the design space. An additional application of ContCarSim involves the generation of datasets for data analytics, operation design and process monitoring studies.

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