Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Engineering

Review

Advanced methodologies for model-based optimization and control of pharmaceutical processes

Francesco Destro*, Pavan K Inguva*, Prakitr Srisuma* and Richard D Braatz

Traditionally, the pharmaceutical industry relied on resource-intensive and empirical methods for process development, optimization, and control. Heuristic approaches to pharmaceutical development and manufacturing have led to an unsustainable number of drug shortages and recalls and to escalating costs for launching new drug products. Optimization and control strategies rooted on process modeling are helping to advance pharmaceutical manufacturing by reducing development times and manufacturing costs, improving productivity and quality control, and enhancing process understanding. This perspective discusses recent developments toward model-based optimization, state estimation, and control of pharmaceutical processes. Ancillary areas such as software tools, equipment and sensor technology, and process modeling are first covered. Then, several recent academic and industrial case studies are discussed to highlight workflows and benefits related to the implementation of model-based optimization, state estimation, and control in (bio)pharmaceutical manufacturing. Finally, strategies for overcoming current challenges in the real-world application of model-based optimization and control are discussed.

Address
Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Corresponding author: Braatz, Richard D (braatz@mit.edu)
* Co-first authors.

Current Opinion in Chemical Engineering 2024, **45**:101035

This review comes from a themed issue on **Pharmaceutical Manufacturing**

Edited by **Kimberley B. McAuley, Salvador García Muñoz** and **Jonathan McMullen**

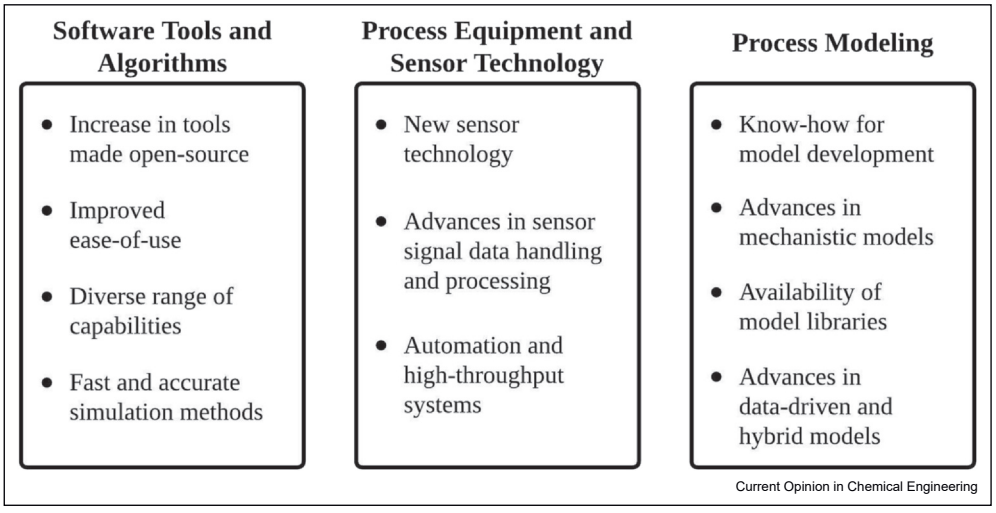
Available online xxxx

https://doi.org/10.1016/j.coche.2024.101035

Introduction

The formal definition of process optimization entails a well-defined mathematical procedure by which an economic objective function is optimized under a set of constraints [1]. Within most manufacturing sectors, process optimization is routinely applied to identify the operating conditions that maximize the efficiency and the productivity of a process under given quality constraints [2]. In pharmaceutical manufacturing, the term 'process optimization' typically refers to a broad set of activities that are conducted for enhancing a process, not necessarily involving mathematical optimization [3]. Historically, pharmaceutical process development was carried out with heuristic approaches, prioritizing speed over efficiency and robustness, to timely scale up processes for new products to clinical trial volumes and then to commercial scale [4]. Even today, design of experiments and response surface methodology are the most widely used approaches for process enhancement in the pharmaceutical sector [5]. A similar lag between the pharmaceutical industry and other industries exists in terms of advanced process control, with most pharmaceutical processes lacking the implementation of feedback control of the product quality variables [3,5,6]. These limitations in pharmaceutical manufacturing contribute to the large number of shortages and recalls of drug products that have recently been registered, as well as to escalating costs for bringing new pharmaceuticals to the market [7,8]. In response to these issues, the pharmaceutical industry accelerated its modernization efforts, driven by regulatory initiatives, such as current good manufacturing practices [9], process analytical technology (PAT) [10], and quality by design (QbD) [11,12]. QbD represents a departure from traditional quality-by-testing methods, adopting a scientific and risk-based approach to ensure consistent production of high-quality drugs. PAT enhances the QbD framework by enabling real-time monitoring of critical process variables through advanced sensors, unlocking the potential to achieve real-time release testing. Within the recent interest in improving efficiency and quality in pharmaceutical manufacturing, process development and manufacturing workflows can benefit from the adoption of process optimization and control approaches

Figure 1



Summary of recent drivers in advancing modeling and model-based optimization and control of pharmaceutical manufacturing processes.

based on mathematical models, as advocated by regulators [13,14]. This article reviews advances in methodologies and applications of model-based optimization and control of pharmaceutical processes, with a focus on contributions published within the past 5 years. Earlier progress toward model-based optimization and control of pharmaceutical processes and a comprehensive overview of the role of process modeling in QbD are presented elsewhere [15]. The next section summarizes the tools for process optimization and control that are currently available to practitioners, with a focus on both hardware and software capabilities. Then recent studies on model-based optimization and control of pharmaceutical systems are discussed, highlighting emerging trends and potential developments.

Ingredients for optimization and control

This section explores recent advances in the constitutive components of both the construction of a suitable process model and for subsequent application of advanced optimization and control methods. A summary of drivers helping advance the field can be found in Figure 1.

Software tools and algorithms

Recent developments in software tools for modeling, optimization, and control are enabling users to rapidly develop and implement various computational tools into the pharmaceutical process development workflow. Three trends can be observed, which are facilitating the adoption of computational resources and methods:

- **Open source**. Many authors, both from academia and industry, are increasingly making their code publicly available on sites such as GitHub and publishing associated articles outlining the tool. This helps users gain a better understanding of the tool and facilitates modification to suit their needs.
- **Ease-of-use**. Many modern software packages are either being developed entirely in accessible programming languages (e.g. Python, Julia) or have wrappers/interfaces with these languages. Many of these tools also have extensive documentation with helpful examples and active discussion forums where users can get assistance. Developers and advanced users also often develop teaching material using specific packages, which provide another valuable resource (e.g. see Ref. [16]). The development of graphical user interfaces and web apps is also being made easier with modern tools, such as Streamlit [17] and PyQT5 [18].
- **Diverse range of capabilities**. The ecosystem of available software tools is rapidly maturing, with a range of tools for different needs. Examples of excellent software codes released recently are categorized by application: thermodynamics [19,20], partial differential equations [21,22], optimization [23,24], optimal control and model predictive control (MPC) [23,25], and process data analytics [26].

Concomitant advances in methods and algorithms for simulation and optimization are important for driving improvements in software in three domains: stability/convergence, accuracy, and efficiency. In some cases, such as MPC and real-time optimization, the development of highly efficient numerical methods is essential for the application of these techniques in practice. The development of relevant software tools and algorithms can and often does take place in different disciplines (e.g. applied mathematics and physics communities), thus practitioners should strive to keep abreast of

developments in adjacent knowledge domains. Advances in algorithms have been made for all of the classes of model equations that arise in pharmaceutical manufacturing, including differential–algebraic equations (DAEs) and integropartial differential–algebraic equations (IPDAEs). An example is an efficient finite difference method [27,28] for simulating population balance models (PBMs), which are a powerful PDE-based framework for describing systems relevant to pharmaceutical manufacturing such as processes that include cells (e.g. to incorporate cell age/size as an intrinsic variable) or crystals (e.g. to track the evolution of the crystal size distribution). The scheme employs specially constructed transformations to solve the PBM accurately (in some cases to machine precision) with computational costs much lower than higher order methods and alternative techniques (e.g. [29–31]). For control-related applications, a fast technique for solving optimal control problems by reformulation as a system of DAEs has been developed, eliminating the need for an optimization solver and thus speeding up the simulation by more than an order of magnitude [32].

While this section focuses on open-source software, there are several commercial software packages available that have found significant use in the pharmaceutical industry. Some well-known commercial process simulators that have dedicated features for pharmaceutical processes include Aspen Plus (Aspen Technology, Inc.), gPROMS (Siemens AG), and SuperPro Designer (Intelligen, Inc.). Other notable commercial tools for multiphysics/computational fluid dynamics simulations that have found use in the pharmaceutical industry include COMSOL (COMSOL, Inc.), Star-CCM+ (Siemens AG), and ANSYS (Ansys, Inc.). Many of these commercial tools are under active development to incorporate new capabilities to support pharmaceutical applications (e.g. gPROMS Formulated Products). Commercial software providers often have helpful technical notes with exemplar models that are useful as templates and also are resourced to provide direct support to users. The choice of which software tool to use can be complicated but ultimately depends on the nature of the problem at hand and the constraints (e.g. cost/know-how) of the user/organization.

Process equipment and sensor technology

Recent equipment developments have focused on automation and/or lowering sample volume requirements, enabling high-throughput workflows, even for costly products and processes. These developments are taking place for several processes and unit operations, such as powder dispensing [33], pH adjustments for formulation [34], crystallization parameter estimation [35], and multiple steps in both upstream and downstream biomanufacturing [36,37]. In many cases, the technology is already commercially available as turn-key solutions or leverages existing know-how and equipment and can be incorporated into process development workflows relatively quickly. These advances, in particular, those related to automation, will likely become prevalent, even in large-scale manufacturing operations and facilitate the implementation of advanced control strategies, which may require complex process operation (e.g. complex feeding policies for bioreactors). The ability to generate more high-quality data with less resources (both material and manpower) in shorter time frames will accelerate the development of process models.

The advancement and promulgation of sensors and associated technologies (e.g. software/algorithms for signal/data processing) has enabled the real-time and/or inline measurement of process variables and conditions previously deemed inaccessible in various pharmaceutical unit operations. Such tools are invaluable for providing deeper process insights and more accurate experimental data for the construction of mechanistic models and also for facilitating the implementation of more sophisticated process monitoring and control methodologies. Some notable recent developments in sensor technology for pharmaceutical manufacturing applications are as follows:

- NanoFlowSizer by InProcess-LSP [38]: The NanoFlowSizer platform enables the real-time and inline characterization of the particle size distribution (PSD) of nanodispersions in flow. This platform has enabled the inline measurement of the PSD during the continuous manufacturing of nanoparticulate systems (e.g. emulsions formed using high-pressure homogenization [39] and precipitation of lipid nanoparticles and/or liposomes using rapid mixing [40]).
- Inline microscopy: The use of inline microscopy coupled with image processing can generate rich data for analyzing particulate and cell systems. For particulate systems (e.g. for crystallization processes), inline microscopy has successfully been applied to measure properties, such as the PSD and solids concentration [41,42]. For cell systems, the Ovizio iLine platform uses digital holographic microscopy, which can generate both cell images and several image features that can be used to characterize properties, such as cell viability and infection state in the case of viral particle systems [43,44].
- Laser speckle with PEACE [45]: By employing a physics-enhanced machine learning algorithm to analyze the laser speckle from a powder bed, it is possible to obtain real-time noninvasive measurements of the PSD for a range of particulate processes, such as drying, blending, and milling.
- Variable pathlength spectroscopy (VPS): Conventionally, quantification of high-concentration samples required dilution for the measurement to remain in the linear dynamic range. VPS technologies, such as the commercially available SoloVPE (at-line)

and FlowVPX (inline) platforms, use a variable pathlength and slope spectroscopy to enable efficient sample quantification [46,47].

Process modeling

Broadly, the methods for constructing process models can be classified by the extent of physical insight and knowledge captured by the model with mechanistic models that capture mechanistic insights of the process at one end of the spectrum and data-driven models that empirically describe available data at the other end. This review focuses on mechanistic modeling due to its enabling of increased process understanding and the application of model-based optimization and control and because such models can be less expensive to formulate due to lower data requirements. For a discussion of data-driven and hybrid modeling strategies, the interested reader is directed to topic-specific reviews, for example, [48,49]. As practitioners become more adept with model formulation and development, that is, translating mechanistic insight of the process into a mathematical description and validating the model with suitable experimental data, the use of mechanistic models will continue to expand and become more mainstream. Model development should not be carried out in isolation, and close collaboration between modeling and experimental teams creates a synergistic relationship, with experimentalists providing insights that modelers may lack and modelers helping to guide experimental design and data analysis.

Advances in mechanistic modeling fall into two categories: (a) model refinement and improvement and (b) development of novel models. For brevity, we focus on advances in the latter category, and interested readers are directed to the literature for examples on the former (e.g. see Ref. [50] for chromatographic separations and Ref. [51] for high-pressure homogenization). The development of novel mechanistic models primarily is taking place for complex/novel process configurations, for example, microwave-assisted lyophilization (Figure 2a), and emerging modalities, for example, mRNA therapeutics and gene therapy manufacturing (Figure 2b). In both cases, modeling teams need to start from first principles and gain a deep understanding of the process to successfully develop a model since, in many instances, they are developing a first-of-a-kind model. Knowledge from adjacent domains is invaluable for model building and parameter estimation. For example, previous work in epidemiology and viral infection kinetics are useful sources of information for developing process models for viral particle manufacturing [52]. Table 1 lists several novel mechanistic models that have been recently developed for a variety of pharmaceutical processes, with brief discussion. Figure 3a summarizes the workflow for developing a model to be used for optimization and/or control of a pharmaceutical process.

Advances in optimization and control practice

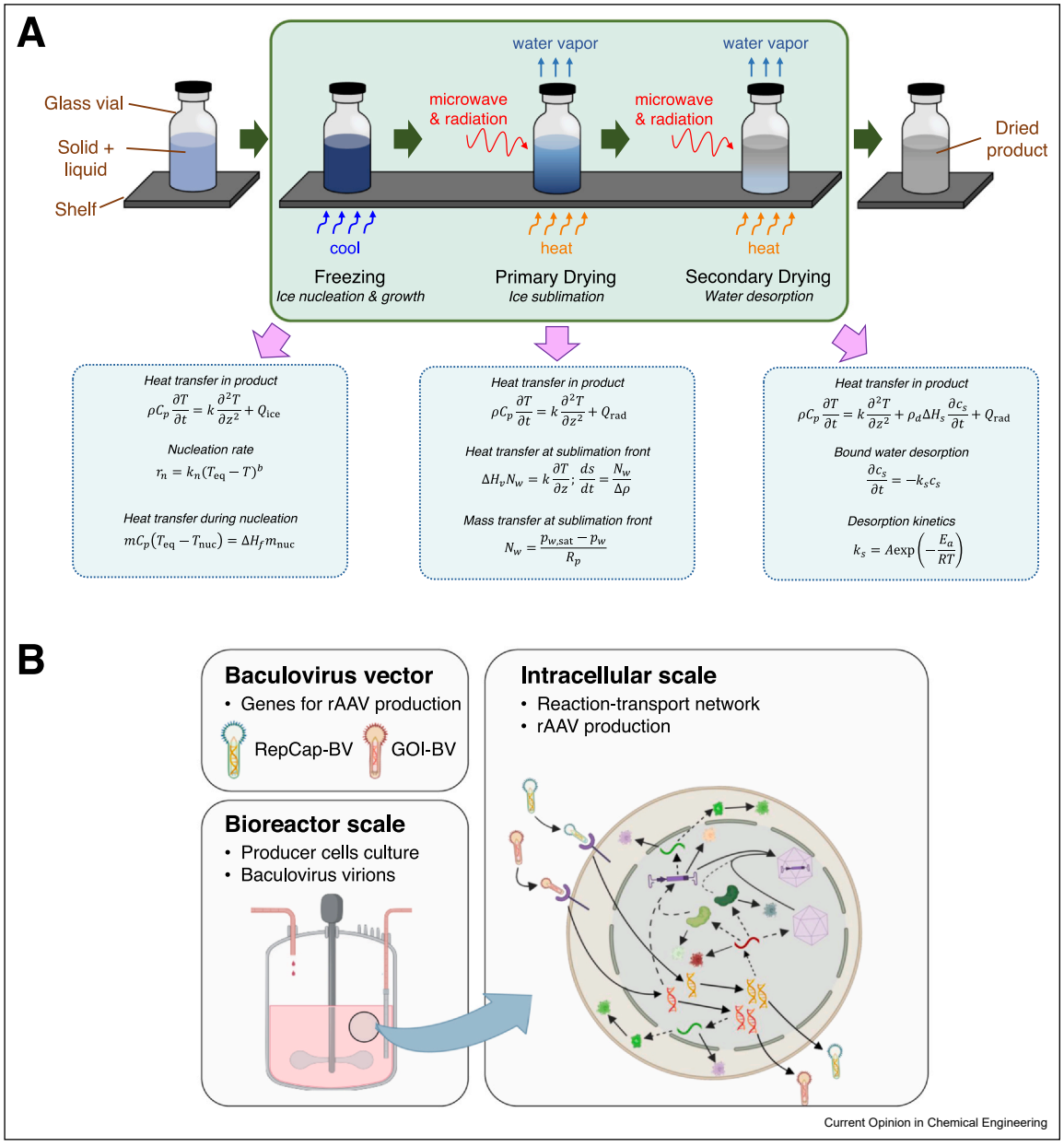
Optimization

Several studies on model-based optimization of individual pharmaceutical unit operations have been presented in the past decade, including for reactors, crystallization, and chromatography [15]. In model-based optimization of a pharmaceutical process, a mathematical model for a unit of interest is first developed and validated with experimental data. Then, the model is used as *in silico* representation of the process for determining the operating conditions that maximize a productivity metric, using either derivative-based or derivative-free algorithms. Multiobjective optimization can be used for determining Pareto fronts that compromise across multiple goals. Although model-based optimization of individual unit operations represented a step forward with respect to earlier heuristic process development, simultaneous model-based design and optimization across multiple units and, eventually, plant-wide optimization, are the ultimate means to deliver next-generation pharmaceutical quality.

Recently, a model was developed for a solid oral-dosage downstream manufacturing process, with interconnected wet granulation, drying, and milling unit operations [63]. The model was validated with experimental data and then used for optimizing the operating conditions, achieving an estimated 83% reduction of energy consumption [64]. Another study recently demonstrated model-based optimization of an end-to-end continuous pharmaceutical process for aspirin manufacturing [65]. Dynamic models were developed and validated for the individual unit operations, which included two-step flow synthesis, crystallization and *in vitro* dissolution of testing of the final product. Notably, plant-wide optimization led to threefold increase in overall productivity and 10% higher conversion compared with step-by-step optimization of individual unit operations. Another recent study exploited nonsmooth dynamic simulation and optimization to maximize the yield and productivity of an *in silico* plant that included recycles from the crystallizer outlet to either the crystallizer or the reactor [66]. The *in silico* plant considered for the dynamic optimization was inspired by an experimental pilot plant operated in the Novartis-MIT Center for Continuous Manufacturing, which, however, did not include recycles in place [67]. Dynamic optimization showed that the introduction of recycles in continuous pharmaceutical manufacturing can increase yield and productivity. On the contrary, optimization of the considered plant through steady-state simulations did not generate a design that met the target product quality specifications.

Pharmaceutical process optimization is strictly connected to the regulatory concept of design space, namely, the feasible space of operating conditions that allow to meet the product quality with an acceptable probability, for given raw material attributes [11]. Several algorithms have

Figure 2



Examples of recently developed mechanistic models of pharmaceutical processes. **(a)** Lyophilization of biotherapeutics. A model describes heat and mass transfer within the product during three phases of lyophilization: freezing, primary drying, and secondary drying. **(b)** Recombinant adeno-associated virus (rAAV) manufacturing in insect cells: multiscale model encompassing the bioreactor scale and resolving the intracellular reaction–transport network that leads to rAAV formation within producer cells. A detailed description of the model is given in Destro et al. [55].

been proposed for design space description through model-based optimization [68], including a recent strategy that exploits derivative-free optimization and process models implemented as black boxes that can be called through commercial simulators [69]. A recent work demonstrated the use of robust optimization for simultaneously defining the probabilistic design space and maximizing productivity therein for continuous integrated filtration–drying of crystallization slurries [70]. Surrogate models, which are simplified models derived from detailed and resource-intensive models, can be useful for constructing design spaces, and, more generally, for optimizing pharmaceutical processes [71,72].

Given the fast pace of pharmaceutical process development, the capability to timely develop a novel process model can become the bottleneck toward the actual implementation of model-based optimization by

Table 1

Some recent advances in mechanistic modeling for pharmaceutical processes.

Process	Description	Reference
In vitro transcription (IVT)	IVT modeling focuses on developing a more complete model that incorporates various complex phenomena that have not been captured by previous models. The model is used to described unexplained trends in the previous IVT literature and help guide future experiments.	[53]
Recombinant adeno-associated virus (rAAV) production	The first models for rAAV manufacturing in mammalian and insect cell cultures were recently developed.	[54,55]
Lyophilization	While models for conventional lyophilization are well established, recent extensions address nonconventional techniques, such as microwave-assisted and continuous lyophilization, and incorporate increased understanding of the freezing step.	[56–61]
Continuous column-based viral inactivation	A model for a novel and low-cost continuous viral inactivation system was recently developed.	[62]

practitioners. Model-based design of experiments can reduce this time [73] by optimizing the informativeness of the data to more quickly converge to the correct underlying mechanisms associated with any poorly understood phenomena [74]. In this context, a 70% reduction of the experimental effort for model-based design of tablet lubrication was recently achieved in a direct compression process through model-based design of experiments [75]. More generally, there is a high potential for platforms that can autonomously plan and/or execute experiments for model development and model-based optimization within pharmaceutical manufacturing systems [76]. In the future, increasing model-based applications in biopharmaceutical manufacturing are expected, given the raising commercial importance of biologics. Within this domain, processes that involve the use of living cells create opportunities for novel optimization approaches, in which intracellular modeling is exploited for optimizing both the process conditions and the genetics of the biological platform for increased productivity, as recently shown [54,55].

State estimation

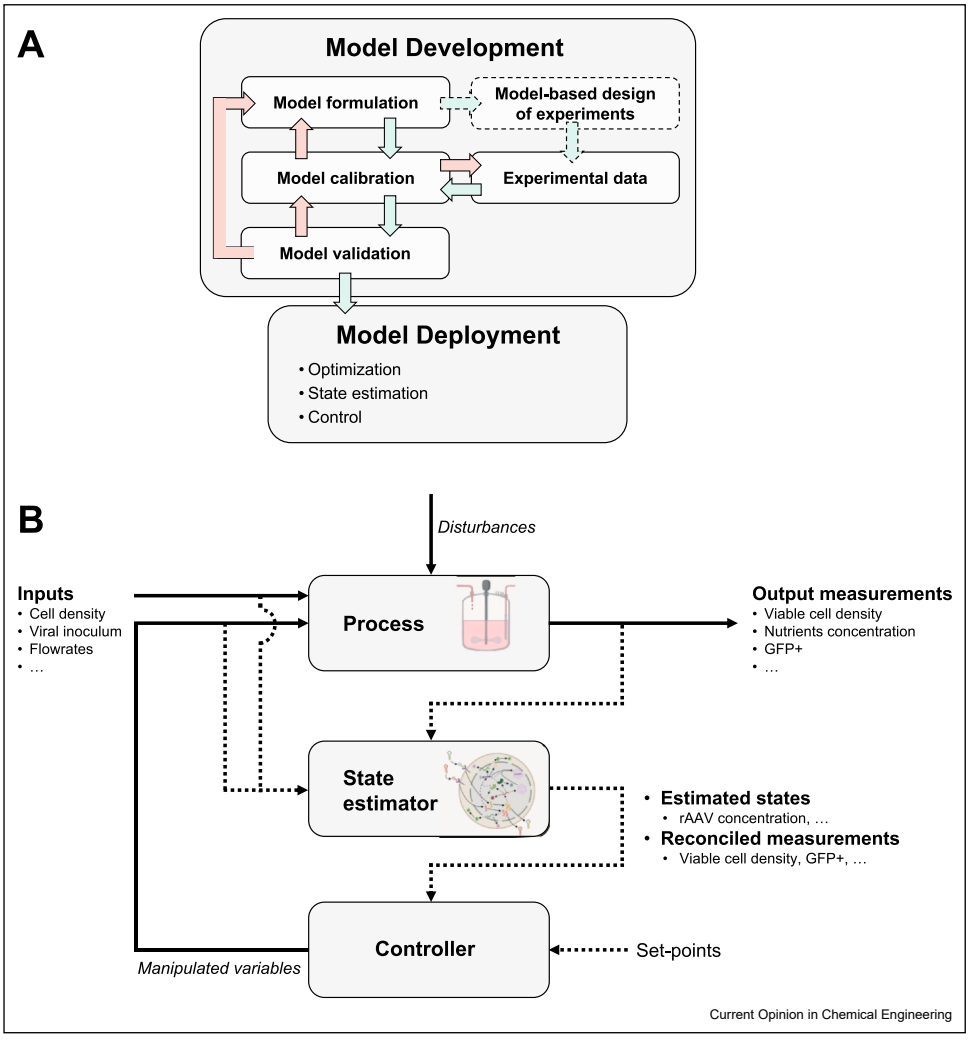
State estimation is a framework for the real-time estimation of the unmeasured states, given the available measurements and mechanistic understanding of a system; a tool that performs state estimation is referred to as a state observer or state estimator, also known as a soft sensor in some fields [77]. Those unmeasured states could be internal states that cannot be measured or states that are difficult (or too expensive) to measure. State estimation is critical for process monitoring and control strategies that require access to any unmeasured states (Figure 3b). In the pharmaceutical industry, a state observer can be integrated with PAT and hence plays an important role in driving and ensuring the successful transition from batch to continuous manufacturing [78,79]. Several well-known observers have been applied in the pharmaceutical industry, including the Luenberger observer, Kalman filter, sliding-mode observer, and moving horizon estimator (MHE); we refer to Refs. [80,81] for detailed discussion of those observers.

State estimation has been explored for various pharmaceutical processes and unit operations. One of the most common unit operations in this context is a fluidized bed dryer for drying wet granules, in which the main objective is to ensure that the residual moisture content in discharged granules is below the required threshold. For this purpose, various observers have been developed to approximate moisture-related quantities in real time, including an MHE for estimating moisture content, given the inlet gas and particle temperature measurements [82] and an extended Kalman filter (EKF) to estimate the drying rate and air humidity [83]. State observers have been demonstrated for process and product quality control, for example, Luenberger and sliding mode observers-based feedback control [84] and MHE-based nonlinear model predictive control (NMPC) [85].

Direct compression for table manufacturing is another process where state estimation has been investigated. A number of soft sensors have been proposed for monitoring of tablet potency, with the use of both mechanistic modeling [86] and hybrid modeling [87], offering alternatives to the traditional monitoring approach with near-infrared spectroscopy. An EKF was developed for a compartmental model that represents the flow in the tablet press; the proposed EKF was shown to accurately estimate the species concentration in real time while efficiently handling sensor noise [79]. A combined MHE-NMPC framework has been developed to help reduce plant-model mismatch effects, for example, caused by uncertain model parameters, in continuous direct compression [88]. State estimation has also been explored for feeding–blending [78] and crystallization [89].

Unlike small molecules, the literature on state estimation for biotherapeutic manufacturing spans decades. While state estimation based on simple bioreactor models using standard design methods is well established, some recent studies have explored other types of bioprocessing units

Figure 3



Model-based optimization and control of pharmaceutical processes. **(a)** Workflow for model development. Green arrows indicate the path after successful completion of a stage, while red arrows show the path if a stage is unsuccessful. Model formulation is the first stage of the workflow and is followed by model calibration with experimental data (i.e. parameter estimation) and by model validation. A validated model can be used for model-based optimization, state estimation, and/or control. Model development is an iterative procedure in which failure (red arrows) in calibration or validation leads to additional steps of model reformulation and/or experimental data collection. Model-based design of experiments can optionally be used at any stage to design experiments that target a specific goal (e.g. increasing model precision). **(b)** Use of state estimation for supporting process monitoring and control, demonstrated through an illustrative example in recombinant adeno-associated virus (rAAV) manufacturing. Dotted lines indicate information flow. GFP = green fluorescent protein.

and novel observers. An example of the former is the use of real-time thermal imaging and a Luenberger observer to estimate the amount of frozen material in a vial during cell thawing, which is the last processing step in cell therapy [90]. An example of the latter is the design of a sliding mode observer for estimating the net growth rate and the glucose consumption rate in continuously perfused HEK-293 cell cultures [91].

State estimation is gaining increasing interest for application to process monitoring and control in pharmaceutical manufacturing. Although the primary aim of state estimation is to estimate unmeasured states, a state observer can also be used for other purposes, such as filtering sensor noise, reducing the effects of plant-model mismatch on model predictions, and estimating parameters. Future state estimation studies could focus more on these three aspects. First, applications to emerging biotherapeutics such as mRNA vaccines should be considered, as most of their states cannot currently be measured in real time. Second, future studies on observer design should more explicitly take the

effects of uncertainties in the model and its initial conditions into account. Many recent studies have assumed that the initial states are all perfectly known during the observer design, which is not true for most (bio)pharmaceutical processes. This deviation can significantly slow the convergence of the estimated states [90], resulting in poorly performing process monitoring and control. Finally, by carefully considering the mathematical structure of the model and observer, some advances in observer design, for example, fast MHE [92], could be used for more efficient and robust state estimation.

Control

In pharmaceutical manufacturing, maintaining the product critical quality attributes (CQAs) within target values is of utmost importance. Regulatory agencies have recently emphasized that implementing active control of CQAs through feedback control enhances the robustness and reliability of control strategies [12,93]. However, pharmaceutical processes are still predominantly operated in open loop with respect to product quality variables due to significant challenges in obtaining online measurements of the CQAs and addressing complex process dynamics, disturbances, and model uncertainties. Recent progress in PAT for online measurement of critical process variables and in active process control is changing this paradigm [6,94,95]. In past years, model-based control has been applied to several pharmaceutical unit operations taken in isolation, such as reactors and crystallization [15]. While implementation on integrated unit operations are not as mature, plant-wide MPC of a pharmaceutical process has been demonstrated in a nonlinear simulation for end-to-end continuous pharmaceutical manufacturing [95]. High-performance control of the CQAs was demonstrated, even in presence of significant model uncertainties and disturbances. Although plant-wide MPC has not yet been implemented on a pharmaceutical manufacturing plant in industry, industrial implementations of model-based control systems have been demonstrated for drug product manufacturing [96]. The use of MPC was successfully demonstrated in a continuous feeding–blending process for rejecting feeder fluctuation disturbances, which is intrinsically a challenging control problem [97]. Advanced MPC algorithms have been demonstrated in academic studies. For example, nonlinear MPC was recently validated in integrated roll compaction and ribbon milling unit operations within a continuous dry granulation line [98]. Better control of mass throughput and output ribbon solid fraction was achieved by the nonlinear MPC than for a classical control system. The MPC was based on a hybrid model, combining a mechanistic compartment for roll compaction with an artificial neural network for milling. Model-based control was also a key enabler for the integration of a crystallizer with a drop-on-demand technology that exploits 3D printing for manufacturing solid dosage forms from a liquid formulation [99]. Continuous connection of the crystallizer with the drop-on-demand platform was established through a three-phase settler, designed to achieve a suspension with controlled concentration of active pharmaceutical ingredient crystals. A case study on continuous manufacturing of the drug lomustine demonstrated that the integrated platform could produce dosages presenting the target dose and dissolution profile. The proposed process has the potential to replace traditional granulation lines, and the associated powder handling issues, for certain applications. Additional applications of MPC and real-time optimization to pharmaceutical unit operations are documented for continuous integrated filtration, washing and drying, and crystallization slurries [100]. An experimentally validated simulator was recently developed and made publicly available for benchmarking novel control systems for these unit operations, including model-free, model-based, and state estimation implementations [101]. These examples showcase significant progress in model-based control of drug product manufacturing and of continuously integrated pharmaceutical unit operations. On the biologics side, recent progress toward the transition to continuous and perfusion implementations of biopharmaceutical processes offer opportunities for model-based control, especially considering recently developed platforms for automated continuous manufacturing of protein-based biopharmaceuticals, such as monoclonal antibodies [102,103]. During the development of a continuous end-to-end platform for monoclonal antibodies manufacturing, process models of the chromatography steps in the downstream section were developed and used for supporting the *in silico* design of the control system [104]. MPC was physically implemented in a continuous viral inactivation system for biologics derived from mammalian cultures [62]. Tight pH control and minimum residence time were achieved through MPC and Bayesian estimation. For both small-molecule and biologic drug manufacturing, future work should focus on further expanding model-based control studies towards the final goal of validating plant-wide MPC.

Outlook

The application of model-based methods for the optimization and control of pharmaceutical processes is broadly acknowledged as the future and has correspondingly received significant commitment from academic, industrial, and regulatory stakeholders. Many efforts by industry and academia are continuing to bear fruit (e.g. see Ref. [105]). Nonetheless, the successful realization of model-based methods across the sector can be challenging due to various reasons, such as technical limitations (e.g. lack of sensors to measure certain process variables rapidly or inefficiency of numerical methods for some classes of models) and inexperience with incorporating modeling into the process development workflow (e.g. inadequate co-ordination between

modeling and experimental teams leading to insufficient or low-quality data being generated for model development).

Considering the uptick in the application of model-based strategies for pharmaceutical processes both in academia and industry and the rapid pace of development in ancillary technologies, it is clear that there is significant momentum, and it is likely model-based methods for optimization and control will become the norm. However, continued work, both in developing new technologies (such as those outlined in *Ingredients for optimization and control*) and strengthening organizational/manpower capabilities is necessary as there are still many challenges to be overcome. Collaborative efforts such as industry–regulatory–academic partnerships and precompetitive consortia (e.g. see Refs. [106,107]) are potentially useful platforms for derisking the development of necessary technologies and establishing sector-wide best practices.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was done in Cambridge, MA, USA. This research was supported by the U.S. Food and Drug Administration under Contract No. 75F40121C00090. Financial support is also acknowledged from the Agency for Science, Technology and Research (A*STAR), Singapore.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Biegler LT, Grossmann IE, Westerberg AW: **Systematic Methods for Chemical Process Design**. Prentice Hall PTR; 1997.

2. Isaksson AJ, Harjunkoski I, Sand G: **The impact of digitalization on the future of control and operations**. *Comput Chem Eng* 2018, **114**:122-129.

3. Grangeia HB, Silva C, Simões SP, Reis MS: **Quality by design in pharmaceutical manufacturing: a systematic review of current status, challenges and future perspectives**. *Eur J Pharm Biopharm* 2020, **147**:19-37.

4. Reinhardt IC, Oliveira JC, Ring DT: **Current perspectives on the development of Industry 4.0 in the pharmaceutical sector**. *J Ind Inf Integr* 2020, **18**:100131.

5. terHorst JP, Turimella SL, Metsers F, Zwiers A: **Implementation of Quality by Design (QbD) principles in regulatory dossiers of medicinal products in the European Union (EU) between 2014 and 2019**. *Ther Innov Regul Sci* 2021, **55**:583-590.

6. Su Q, Ganesh S, Moreno M, Bommireddy Y, Gonzalez M, Reklaitis GV, Nagy ZK: **A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing**. *Comput Chem Eng* 2019, **125**:216-231.

7. Farid SS, Baron M, Stamatis C, Nie W, Coffman J: **Benchmarking biopharmaceutical process development and manufacturing cost contributions to r&d**. *MAbs* (1) 2020, **12**:1754999.

8. Musazzi UM, Di Giorgio D, Minghetti P: **New regulatory strategies to manage medicines shortages in europe**. *Int J Pharm* 2020, **579**:119171.

9. FDA: Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st century — A Risk Based Approach; Technical report, 2004.

10. FDA: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance; Technical report, 2004.

11. International Council for Harmonisation: Q8(R2) — Pharmaceutical Development; Technical report, 2009.

12. Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J: **Understanding pharmaceutical quality by design**. *AAPS J* 2014, **16**:771-783.

13. International Council for Harmonisation: Q8, Q9, Q10 — Points to Consider. Technical report, 2011.

14. FDA: Artificial Intelligence in Drug Manufacturing; Technical report, 2023.

15. Destro F, Barolo M: **A review on the modernization of pharmaceutical development and manufacturing — trends, perspectives, and the role of mathematical modeling**. *Int J Pharm* 2022, **620**:121715.

16. Paoli LT, Inguva PK, Haslam AJ, Walker PJ: **Confronting the thermodynamics knowledge gap: a short course on computational thermodynamics in Julia**. *Educ Chem Eng* 2024, **48**:1-14.

17. Khorasani M, Abdou M, Fernández JH: **Web Application Development With Streamlit**. Apress; 2022.

18. Willman J: **Modern PyQt**. Apres; 2021.

19. •• Walker PJ, Yew H-W, Riedemann A: **Clapeyron.jl: an extensible, open-source fluid thermodynamics toolkit**. *Ind Eng Chem Res* 2022, **61**:7130-7153.
This article outlines the development of Claperyon.jl, an open-source thermodynamics toolkit built in Julia. Claperyon.jl provides an extensible way to implement a wide range of thermodynamic models and methods efficiently and comes with several state-of-the-art models already built in such as the SAFT equation.

20. Rehner P, Bauer G, Gross J: **An open-source framework for equations of state and classical density functional theory**. *Ind Eng Chem Res* 2023, **62**:5347-5357.

21. Burns KJ, Vasil GM, Oishi JS, Lecoanet D, Brown BP: **Dedalus: a flexible framework for numerical simulations with spectral methods**. *Phys Rev Res* 2020, **2**:023068.

22. IA Baratta, JP Dean, JS Dokken, M Habera, JS Hale, CN Richardson, ME Rognes, MW Scroggs, N Sime, and GN Wells: DOLFINx: The Next Generation FEniCS Problem Solving Environment; Zenodo, 2023.

23. Beal LDR, Hill DC, Martin RA, Hedengren JD: **GEKKO optimization suite**. *Processes* 2018, **6**:106.

24. Andersson JAE, Gillis J, Horn G, Rawlings JB, Diehl M: **CasADi: a software framework for nonlinear optimization and optimal control**. *Math Program Comput* 2019, **11**:1-36.

25. • Fiedler F, Karg B, Lüken L, Brandner D, Heinlein M, Brabender F, Lucia S: **do-mpc: towards FAIR nonlinear and robust model predictive control**. *Control Eng Pract* 2023, **140**:105676.
This article outlines the development of do-mpc, an open-source model-predictive control (MPC) software in Python. do-mpc enables the development and implementation of sophisticated MPC controllers,

including nonlinear and robust MPC and incorporates the MHE for state estimation. The developers have taken care to ensure ease-of-use while also enabling deep customization.

26. Sun W, Braatz RD: **Smart process analytics for predictive modeling**. *Comput Chem Eng* 2021, **144**:107134.

27. Inguva PK, Schickel KC, Braatz RD: **Efficient numerical schemes for population balance models**. *Comput Chem Eng* 2022, **162**:107808.

28. Inguva PK, Braatz RD: **Efficient numerical schemes for multidimensional population balance models**. *Comput Chem Eng* 2023, **170**:108095.

29. Omar HM, Rohani S: **Crystal population balance formulation and solution methods: a review**. *Cryst Growth Des* 2017, **17**:4028-4041.

30. Shu YD, Liu JJ, Zhang Y, Wang XZ: **Considering nucleation, breakage and aggregation in morphological population balance models for crystallization processes**. *Comput Chem Eng* 2020, **136**:106781.

31. Singh M, Ranade V, Shardt O, Matsoukas T: **Challenges and opportunities concerning numerical solutions for population balances: a critical review**. *J Phys A Math Theor* 2022, **55**:383002.

32. P Srisuma, G Barbastathis, and RD Braatz : **Simulation-Based Approach for Optimal Control of a Stefan Problem**; In: American Control Conference, 2024. In press.

33. Bahr MN, Damon DB, Yates SD, Chin AS, Christopher JD, Cromer S, Perrotto N, Quiroz J, Rosso V: **Collaborative evaluation of commercially available automated powder dispensing platforms for high-throughput experimentation in pharmaceutical applications**. *Org Process Res Dev* 2018, **22**:1500-1508.

34. Chitre A, Cheng J, Ahamed S, Querimit RCM, Zhu B, Wang K, Wang L, Hippalgaonkar K, Lapkin AA: **pHbot: self-driven robot for pH adjustment of viscous formulations via physics-informed-ML**. *Chem Methods* 2024, **4**:e202300043.

35. Arruda RJ, Cally PAJ, Wylie A, Shah N, Joel I, Leff ZA, Clark A, Fountain G, Neves L, Kratz J, Thorat AA, Marziano I, Rose PR, Girard KP, Capellades G: **Automated and material-sparing workflow for the measurement of crystal nucleation and growth kinetics**. *Cryst Growth Des* 2023, **23**:3845-3861.

36. Doulgkeroglou M-N, DiNubila A, Niessing B, König N, Schmitt RH, Damen J, Szilvassy SJ, Chang W, Csontos L, Louis S, Kugelmeier P, Ronfard V, Bayon Y, Zeugolis DI: **Automation, monitoring, and standardization of cell product manufacturing**. *Front Bioeng Biotechnol* 2020, **8**:811.

37. Silva TC, Eppink M, Ottens M: **Automation and miniaturization: enabling tools for fast, high-throughput process development in integrated continuous biomanufacturing**. *J Chem Technol Biotechnol* 2022, **97**:2365-2375.

38. Besseling R, Damen M, Wijgergangs J, Hermes M, Wynia G, Gerich A: **New unique PAT method and instrument for real-time inline size characterization of concentrated, flowing nanosuspensions**. *Eur J Pharm Sci* 2019, **133**:205-213.

39. Rooimans T, Damen M, Markesteijn CMA, Schuurmans CCL, de Zoete NHC, van Hasselt PM, Hennink WE, van Nostrum CF, Hermes M, Besseling R, Vromans H: **Development of a compounded propofol nanoemulsion using multiple non-invasive process analytical technologies**. *Int J Pharm* 2023, **640**:122960.

40. Sheybanifard M, Guerzoni LPB, Omidinia-Anarkoli A, De Laporte L, Buyel J, Besseling R, Damen M, Gerich A, Lammers T, Metselaar JM: **Liposome manufacturing under continuous flow conditions: towards a fully integrated set-up with in-line control of critical quality attributes**. *Lab a Chip* 2023, **23**:182-194.

41. Vancleef A, Maes D, Van Gerven T, Thomassen LCJ, Braeken L: **Flow-through microscopy and image analysis for crystallization processes**. *Chem Eng Sci* 2022, **248**:117067.

42. Jiang M, Braatz RD: **Low-cost noninvasive real-time imaging for tubular continuous-flow crystallization**. *Chem Eng Technol* 2018, **41**:143-148.

43. Altenburg JJ, Klaverdijk M, Cabosart D, Desmecht L, Brunekreeft-Terlouw SS, Both J, Tegelbeckers VIP, Willekens MLPM, van Oosten L, Hick TAH, van der Aalst TMH, Pijlman GP, van Oers MM, Wijffels RH, Martens DE: **Real-time online monitoring of insect cell proliferation and baculovirus infection using digital differential holographic microscopy and machine learning**. *Biotechnol Prog* 2023, **39**:e3318.

44. Pais DAM, Galrão PRS, Kryzhanska A, Barbau J, Isidro IA, Alves PM: **Holographic imaging of insect cell cultures: online non-invasive monitoring of adeno-associated virus production and cell concentration**. *Processes* 2020, **8**:487.

45. • Zhang Q, Gamekkanda JC, Pandit A, Tang W, Papageorgiou C, Mitchell C, Yang Y, Schwaerzler M, Oyetunde T, Braatz RD, Myerson AS, Barbastathis G: **Extracting particle size distribution from laser speckle with a physics-enhanced autocorrelation-based estimator (PEACE)**. *Nat Commun* 2023, **14**:1159.
This article describes the development of a novel, non-invasive sensor for measuring the PSD of a powder bed in real time. This technology enables the development of advanced process monitoring and control strategies for a variety of unit operations involving powders such as drying, blending, milling, and granulation.

46. McKechnie WS, Tugcu N, Kandula S: **Accurate and rapid protein concentration measurement of in-process, high concentration protein pools**. *Biotechnol Prog* 2018, **34**:1234-1241.

47. Zhang Y, Qi P: **Determination of free sulfhydryl contents for proteins including monoclonal antibodies by use of SoloVPE**. *J Pharm Biomed Anal* 2021, **201**:114092.

48. Sokolov M, vonStosch M, Narayanan H, Feidl F, Butté A: **Hybrid modeling — a key enabler towards realizing digital twins in biopharma?** *Curr Opin Chem Eng* 2021, **34**:100715.

49. Tsopanoglou A, JiménezdelVal I: **Moving towards an era of hybrid modelling: advantages and challenges of coupling mechanistic and data-driven models for upstream pharmaceutical bioprocesses**. *Curr Opin Chem Eng* 2021, **32**:100691.

50. Kumar V, Lenhoff AM: **Mechanistic modeling of preparative column chromatography for biotherapeutics**. *Annu Rev Chem Biomol Eng* 2020, **11**:235-255.

51. Inguva P, Grasselli S, Heng PWS: **High pressure homogenization — an update on its usage and understanding**. *Chem Eng Res Des* 2024, **202**:284-302.

52. Canova CT, Inguva PK, Braatz RD: **Mechanistic modeling of viral particle production**. *Biotechnol Bioeng* 2023, **120**:629-641.

53. Stover NM, Ganko K, Braatz RD: **Mechanistic modeling of in vitro transcription incorporating effects of magnesium pyrophosphate crystallization**. *Biotechnol Bioeng* 2024,1-12.

54. • Nguyen TNT, Sha S, Hong MS, Maloney AJ, Barone PW, Neufeld C, Wolfrum J, Springs SL, Sinskey AJ, Braatz RD: **Mechanistic model for production of recombinant adeno-associated virus via triple transfection of HEK293 cells**. *Mol Ther Methods Clin Dev* 2021, **21**:642-655.
First mechanistic model for rAAV production in HEK293 cells via transient triple transfection. The model encompasses the steps of plasmid-mediated gene delivery and rAAV formation.

55. • Destro F, Joseph J, Srinivasan P, Kanter JM, Neufeld C, Wolfrum JM, Barone PW, Springs SL, Sinskey AJ, Cecchini S, Kotin RM, Braatz RD: **Mechanistic modeling explains the production dynamics of recombinant adeno-associated virus with the baculovirus expression vector system**. *Mol Ther Methods Clin Dev* 2023, **30**:122-146.
First mechanistic model for rAAV production in insect cells via the baculovirus expression vector system. The model encompasses the steps of baculovirus-mediated gene delivery and rAAV formation within baculovirus-infected cells.

56. Nastaj JF, Witkiewicz K: **Mathematical modeling of the primary and secondary vacuum freeze drying of random solids at microwave heating**. *Int J Heat Mass Transf* 2009, **52**:4796-4806.

57. Park J, Cho JH, Braatz RD: **Mathematical modeling and analysis of microwave-assisted freeze-drying in**

biopharmaceutical applications. *Comput Chem Eng* 2021, **153**:107412.

58. Deck LT, Ochsenbein DR, Mazzotti M: **Stochastic shelf-scale modeling framework for the freezing stage in freeze-drying processes**. *Int J Pharm* 2022, **613**:121276.

59. Deck LT, Ochsenbein DR, Mazzotti M: **Stochastic ice nucleation governs the freezing process of biopharmaceuticals in vials**. *Int J Pharm* 2022, **625**:122051.

60. • Srisuma P, Barbastathis G, Braatz RD: **Analytical solutions for the modeling, optimization, and control of microwave-assisted freeze drying**. *Comput Chem Eng* 2023, **177**:108318.
This article derives analytical solutions to the mechanistic model of conventional, microwave-assisted, and hybrid lyophilization. The analytical solutions are much more computationally efficient than numerical solutions.

61. Srisuma P, Barbastathis G, Braatz RD: **Mechanistic modeling and analysis of thermal radiation in conventional, microwave-assisted, and hybrid freeze drying for biopharmaceutical manufacturing**. *Int J Heat Mass Transf* 2024, **221**:125023.

62. Hong MS, Lu AE, Ou RW, Wolfrum JM, Springs SL, Sinskey AJ, Braatz RD: **Model-based control for column-based continuous viral inactivation of biopharmaceuticals**. *Biotechnol Bioeng* 2021, **118**:3215-3224.

63. Sampat C, Kotamarthy L, Bhalode P, Chen Y, Dan A, Parvani S, Dholakia Z, Singh R, Glasser BJ, Ierapetritou M, Ramachandran R: **Enabling energy-efficient manufacturing of pharmaceutical solid oral dosage forms via integrated techno-economic analysis and advanced process modeling**. *J Adv Manuf Process* 2022, **4**:e10136.

64. Chen Y, Kotamarthy L, Dan A, Sampat C, Bhalode P, Singh R, Glasser BJ, Ramachandran R, Ierapetritou M: **Optimization of key energy and performance metrics for drug product manufacturing**. *Int J Pharm* 2023, **631**:122487.

65. • Nagy B, Szilágyi B, Domokos A, Vészi B, Tacsi K, Rapi Z, Pataki H, Marosi G, Nagy ZK, Nagy ZK: **Dynamic flowsheet model development and digital design of continuous pharmaceutical manufacturing with dissolution modeling of the final product**. *Chem Eng J* 2021, **419**:129947.
Demonstration of plant-wide dynamic optimization of a continuous pharmaceutical manufacturing process using an experimentally validated model.

66. • Patrascu M, Barton PI: **Optimal dynamic continuous manufacturing of pharmaceuticals with recycle**. *Ind Eng Chem Res* 2019, **58**:13423-13436.
First application of nonsmooth dynamic optimization to maximize the yield and productivity of an in silico pharmaceutical plant that includes recycles. Dynamic optimization achieves significantly improved performance compared over steady-state optimization.

67. Mascia S, Heider PL, Zhang H, Lakerveld R, Benyahia B, Barton PI, Braatz RD, Cooney CL, Evans JMB, Jamison TF, Jensen KF, Myerson AS, Trout BL: **End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation**. *Angew Chem* 2013, **125**:12585-12589.

68. Zhao F, Ochoa MP, Grossmann IE, García-Muñoz S, Stamatis SD: **Novel formulations of flexibility index and design centering for design space definition**. *Comput Chem Eng* 2022, **166**:107969.

69. Zhao F, Grossmann IE, García-Muñoz S, Stamatis SD: **Flexibility index of black-box models with parameter uncertainty through derivative-free optimization**. *AIChE J* 2021, **67**:e17189.

70. Destro F, Hur I, Wang V, Abdi M, Feng X, Wood E, Coleman S, Firth P, Barton A, Barolo M, Nagy ZK: **Mathematical modeling and digital design of an intensified filtration-washing-drying unit for pharmaceutical continuous manufacturing**. *Chem Eng Sci* 2021, **244**:116803.

71. Boukouvala F, Ierapetritou MG: **Surrogate-based optimization of expensive flowsheet modeling for continuous pharmaceutical manufacturing**. *J Pharm Innov* 2013, **8**:131-145.

72. Castaldello C, Facco P, Bezzo F, Georgakis C, Barolo M: **Data-driven tools for the optimization of a pharmaceutical process through its knowledge-driven model**. *AIChE J* 2023, **69**:e17925.

73. Franceschini G, Macchietto S: **Model-based design of experiments for parameter precision: state of the art**. *Chem Eng Sci* 2008, **63**:4846-4872.

74. Shahmohammadi A, McAuley KB: **Sequential model-based A- and V-optimal design of experiments for building fundamental models of pharmaceutical production processes**. *Comput Chem Eng* 2019, **129**:106504.

75. Cenci F, Bano G, Christodoulou C, Vueva Y, Zomer S, Barolo M, Bezzo F, Facco P: **Streamlining tablet lubrication design via model-based design of experiments**. *Int J Pharm* 2022, **614**:121435.

76. Barhate Y, Kilari H, Wu W-L, Nagy ZK: **Population balance model enabled digital design and uncertainty analysis framework for continuous crystallization of pharmaceuticals using an automated platform with full recycle and minimal material use**. *Chem Eng Sci* 2024, **287**:119688.

77. Patwardhan SC, Prakash J, Shah SL: **Soft sensing and state estimation: review and recent trends**. *IFAC Proc Vol* 2007, **40**:65-72.

78. Liu J, Su Q, Moreno M, Laird C, Nagy Z, Reklaitis G: **Robust state estimation of feeding-blending systems in continuous pharmaceutical manufacturing**. *Chem Eng Res Des* 2018, **134**:140-153.

79. Pablo J, Molina G, Cogoni G, Peeters E, Ambati SR, Nopens I: **A hybrid model for multipoint real time potency observation in continuous direct compression manufacturing operations**. *Int J Pharm* 2022, **613**:121385.

80. A Radke and Z Gao : A Survey of State and Disturbance Observers for Practitioners**,** in: *American Control Conference*; 2006: 5183–5188.

81. Ali JM, Hoang NH, Hussain MA, Dochain D: **Review and classification of recent observers applied in chemical process systems**. *Comput Chem Eng* 2015, **76**:27-41.

82. • M.O. Roseberry, F. Gagnon, A. Desbiens, J. Bouchard, and P.P. Lapointe-Garant: Monitoring the moisture content in pharmaceutical batch fluidized bed dryers using observer-based soft sensors, in: *IFAC-PapersOnLine*; 2020: 53, 12056–12061..
This paper proposes a MHE for estimating the moisture content in a fluidized bed dryer. Various mechanistic models and estimators are compared and discussed. Validation with a pilot-scale dryer shows that the proposed estimators accuratley predict the moisture content.

83. F. Destro, A.J. Salmon, P. Facco, C.C. Pantelides, F. Bezzo, and M. Barolo: Monitoring a segmented fluid bed dryer by hybrid data-driven/knowledge-driven modeling, in: *IFAC-Papers OnLine*; 2020: 53, 11638–11643. https://www.sciencedirect.com/science/article/pii/S240589632030954X.

84. R. Dürr, C. Neugebauer, S. Palis, A. Bück, and A. Kienle: Inferential control of product properties for fluidized bed spray granulation layering, in: *IFAC-Papers OnLine*; 2020: 53, 11410–11415. https://www.sciencedirect.com/science/article/pii/S2405896320308776.

85. Gagnon F, Desbiens A, Poulin É, Lapointe-Garant PP, Simard JS: **Nonlinear model predictive control of a batch fluidized bed dryer for pharmaceutical particles**. *Control Eng Pract* 2017, **64**:88-101.

86. • Kamyar R, Pla DL, Husain A, Cogoni G, Wang Z: **Soft sensor for real-time estimation of tablet potency in continuous direct compression manufacturing operation**. *Int J Pharm* 2021, **602**:120624.
This article proposes a soft sensor based on first-principles and empirical models for real-time monitoring of tablet potency during continuous direct compression. The sensor is able to accurately estimate the tablet potency in various experiments. The work demonstrates the use of state estimation in a practical industrial application.

87. Cogoni G, Liu YA, Husain A, Alam MA, Kamyar R: **A hybrid NIR-soft sensor method for real time in-process control during**

continuous direct compression manufacturing operations. *Int J Pharm* 2021, **602**:120620.

88. Huang YS, Sheriff MZ, Bachawala S, Gonzalez M, Nagy ZK, Reklaitis GV: **Evaluation of a combined mhe-nmpc approach to handle plant-model mismatch in a rotary tablet press**. *Processes* 2021, **9**:1612.

89. Szilagyi B, Nagy ZK: **Real-time feasible model-based crystal size and shape control of crystallization processes**. *Comput Aided Chem Eng* 2019, **46**:1273-1278.

90. Srisuma P, Pandit A, Zhang Q, Hong MS, Gamekkanda J, Fachin F, Moore N, Djordjevic D, Schwaerzler M, Oyetunde T, Tang W, Myerson AS, Barbastathis G, Braatz RD: **Thermal imaging-based state estimation of a Stefan problem with application to cell thawing**. *Comput Chem Eng* 2023, **173**:108179.

91. Abbate T, Sbarciog M, Dewasme L, Wouwer AV: **Experimental validation of a cascade control strategy for continuously perfused animal cell cultures**. *Processes* (4) 2020, **8**:413.

92. Jang H, Lee JH, Braatz RD, Kim KKK: **Fast moving horizon estimation for a two-dimensional distributed parameter system**. *Comput Chem Eng* 2014, **63**:159-172.

93. Fisher AC, Kamga M-H, Agarabi C, Brorson K, Lee SL, Yoon S: **The current scientific and regulatory landscape in advancing integrated continuous biopharmaceutical manufacturing**. *Trends Biotechnol* 2019, **37**:253-267.

94. Simon LL, Pataki H, Marosi G, Meemken F, Hungerbühler K, Baiker A, Tummala S, Glennon B, Kuentz M, Steele G, *et al*.: **Assessment of recent process analytical technology (pat) trends: a multiauthor review**. *Org Process Res Dev* 2015, **19**:3-62.

95. •• Mesbah A, Paulson JA, Lakerveld R, Braatz RD: **Model predictive control of an integrated continuous pharmaceutical manufacturing pilot plant**. *Org Process Res Dev* 2017, **21**:844-854.
First demonstration of plant-wide model predictive control in a nonlinear simulation of an end-to-end continuous pharmaceutical process.

96. Jelsch M, Roggo Y, Brewer M, Géczi ZA, Heger P, Kleinebudde P, Krumme M: **Advanced process automation of a pharmaceutical continuous wet granulation line: perspectives on the application of a model predictive control from solid feeders to dryer**. *Powder Technol* 2023, **429**:118936.

97. Celikovic S, Kirchengast M, Rehrl J, Kruisz J, Sacher S, Khinast J, Horn M: **Model predictive control for continuous pharmaceutical feeding blending units**. *Chem Eng Res Des* 2020, **154**:101-114.

98. Huang Y-S, Lagare RB, Bailey P, Sixon D, Gonzalez M, Nagy ZK, Reklaitis GV: **Hybrid model development and nonlinear model predictive control implementation for continuous dry granulation process**. *Comput Chem Eng* 2024, **183**:108586.

99. • Sundarkumar V, Nagy ZK, Reklaitis GV: **Small-scale continuous drug product manufacturing using dropwise additive manufacturing and three phase settling for integration with upstream drug substance production**. *J Pharm Sci* 2022, **111**:2330-2340.
First demonstration of continuous drug product manufacturing through the integration of a crystallizer with a platform for 3D printing of oral solid dosage forms. Model-based control of the process operation allowed the manufacture of drug product meeting the target dose and dissolution profile.

100. Destro F, Barolo M, Nagy ZK: **Quality-by-control of intensified continuous filtration-drying of active pharmaceutical ingredients**. *AIChE J* 2023, **69**:e17926.

101. Destro F, Nagy ZK, Barolo M: **A benchmark simulator for quality-by-design and quality-by-control studies in continuous pharmaceutical manufacturing — intensified filtration-drying of crystallization slurries**. *Comput Chem Eng* 2022, **163**:107809.

102. Crowell LE, Lu AE, Love KR, Stockdale A, Timmick SM, Wu D, Wang YA, Doherty W, Bonnyman A, Vecchiarello N, Goodwine C, Bradbury L, Brady JR, Clark JJ, Colant NA, Cvetkovic A, Dalvie NC, Liu D, Liu Y, Mascarenhas CA, Matthews CB, Mozdzierz NJ, Shah KA, Wu SL, Hancock WS, Braatz RD, Cramer SM, Love JC: **On-demand manufacturing of clinical-quality biopharmaceuticals**. *Nat Biotechnol* 2018, **36**:988-995.

103. Feidl F, Vogg S, Wolf M, Podobnik M, Ruggeri C, Ulmer N, Wälchli R, Souquet J, Broly H, Butté A, Morbidelli M: **Process-wide control and automation of an integrated continuous manufacturing platform for antibodies**. *Biotechnol Bioeng* 2020, **117**:1367-1380.

104. Gomis-Fons J, Schwarz H, Zhang L, Andersson N, Nilsson B, Castan A, Solbrand A, Stevenson J, Chotteau V: **Model-based design and control of a small-scale integrated continuous end-to-end mAb platform**. *Biotechnol Prog* 2020, **36**:e2995.

105. Ramos I, Sharda N, Villafana R, Hill-Byrne K, Cai K, Pezzini J, Coffman J: **Fully integrated downstream process to enable next-generation manufacturing**. *Biotechnol Bioeng* 2023, **120**:1869-1881.

106. Welch CJ, Faul MM, Tummala S, Papageorgiou CD, Hicks F, Hawkins JM, Thomson N, Cote A, Bordawekar S, Wittenberger SJ, Laffan D, Purdie M, Boulas P, Irdam E, Horspool K, Yang B-S, Tom J, Fernandez P, Ferretti A, May S, Seibert K, Wells K, McKeown R: **The Enabling Technologies Consortium (ETC): fostering precompetitive collaborations on new enabling technologies for pharmaceutical research and development**. *Org Process Res Dev* 2017, **21**:414-419.

107. Erickson J, Baker J, Barrett S, Brady C, Brower M, Carbonell R, Charlebois T, Coffman J, Connell-Crowley L, Coolbaugh M, Fallon E, Garr E, Gillespie C, Hart R, Haug A, Nyberg G, Phillips M, Pollard D, Qadan M, Ramos I, Rogers K, Schaefer G, Walther J, Lee K: **End-to-end collaboration to transform biopharmaceutical development and manufacturing**. *Biotechnol Bioeng* 2021, **118**:3302-3312.