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.

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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.

Software tools and Algorithms

<table>
<thead>
<tr>
<th>Process Equipment and Sensor Technology</th>
<th>Process Modeling</th>
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<tbody>
<tr>
<td>- Increase in tools made open-source</td>
<td>- Know-how for model development</td>
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<tr>
<td>- Improved ease-of-use</td>
<td>- Advances in mechanistic models</td>
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<td>- Diverse range of capabilities</td>
<td>- Availability of model libraries</td>
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<tr>
<td>- Fast and accurate simulation methods</td>
<td>- Advances in data-driven and hybrid models</td>
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Figure 1

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

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 (PBM), 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 Ovízio 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 an *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
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...
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

Table 1
Some recent advances in mechanistic modeling for pharmaceutical processes.

<table>
<thead>
<tr>
<th>Process</th>
<th>Description</th>
<th>Reference</th>
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<tbody>
<tr>
<td>In vitro transcription (IVT)</td>
<td>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 describe unexplained trends in the previous IVT literature and help guide future experiments.</td>
<td>[53]</td>
</tr>
<tr>
<td>Recombinant adeno-associated virus (rAAV)</td>
<td>The first models for rAAV manufacturing in mammalian and insect cell cultures were recently developed. 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.</td>
<td>[54,55]</td>
</tr>
<tr>
<td>Production Lyophilization</td>
<td>A model for a novel and low-cost continuous viral inactivation system was recently developed.</td>
<td>[52]</td>
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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.

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References and recommended reading

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

- of special interest
- of outstanding interest

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.


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 efficient process monitoring and control strategies for a variety of unit operations involving powders such as drying, blending, milling, and granulation.


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.


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.


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60. Srismusa 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.


Demonstration of plant-wide dynamic optimization of a continuous pharmaceutical manufacturing process using an experimentally validated model.


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.


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.


