Digital Chemical Engineering 14 (2025) 100208

Contents lists available at ScienceDirect

Digital Chemical Engineering

journal homepage: www.elsevier.com/locate/dche

Review article

Applications of machine learning for modeling and advanced control of crystallization processes: Developments and perspectives

Fernando Arrais R.D. Lima [a,b], Marcellus G.F. de Moraes [c,d,*], Amaro G. Barreto Jr [a], Argimiro R. Secchi [a,d], Martha A. Grover [b], Maurício B. de Souza Jr [a,d]

[a] Escola de Química, EPQB, Universidade Federal do Rio de Janeiro, P.O. Box 68542, Rio de Janeiro, RJ, 21941-909, Brazil
[b] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, 30332, GA, United States
[c] Instituto de Química, Rio de Janeiro State University (UERJ), Rua São Francisco Xavier, 524, Maracanã, Rio de Janeiro, RJ, 20550-900, Brazil
[d] Programa de Engenharia Química, PEQ/COPPE, Universidade Federal do Rio de Janeiro, PO Box 68502, Rio de Janeiro, RJ, 21941-972, Brazil

ARTICLE INFO

Keywords:
Crystallization models
Crystallization control
Machine learning
Hybrid models
Reinforcement learning
Nonlinear model predictive control

ABSTRACT

Crystallization is a separation method relevant to the production of medicines, food and many other products. An efficient crystallization process must obtain a product with the desired size, length, and purity. Therefore, models and control schemes are applied to achieve this goal. Artificial intelligence techniques, such as machine learning (ML), are applied for modeling and controlling these processes. The current review aims to present the use of ML for modeling and advanced control of crystallization processes. Considering modeling crystallization processes, this paper presents the advances and different uses of ML, such as neural networks, symbolic regression, and transformer algorithms. This review also presents the development of hybrid models combining ML with physical laws for crystallization processes. For the advanced control of crystallization processes, this review presents the development of advanced control strategies based on ML approaches, such as applying neural networks in a nonlinear model predictive controller and based on reinforcement learning. This work can be a relevant reference for the progress of the application of ML in the process systems engineering (PSE) to crystallization processes. It is also expected to encourage industry and academy to use these approaches for different crystallization processes.

1. Introduction

Crystallization, a fundamental process utilized across various industries such as pharmaceuticals, food, and others, involves complex phenomena including nucleation, growth, and phase transitions. Traditionally, understanding and controlling these processes has been challenging due to the complex nature of the mechanisms involved (Gao et al., 2017). Significant research has focused on model-based optimization and control of crystallization processes in the last two decades. The combination of classical control methods with advanced model-based strategies enables more robust, adaptable crystallization processes capable of maintaining high-quality standards across various operational conditions. The relevance of advanced control strategies in crystallization is becoming increasingly evident.

Advances in crystallization control were first investigated by Nagy and Braatz (2003), who developed a robust nonlinear model predictive control (NMPC) approach for batch processes. Their study applied advanced control algorithms to crystallization systems, addressing the challenges posed by uncertainties in kinetic parameters. Braatz (2002) and Nagy et al. (2004) provided a comprehensive overview of significant developments in the modeling and control of batch crystallizers. Their review highlighted key trends regarding crystal size distribution and advancements in sensor technology, computational power, and control algorithms, underscoring the progress made in understanding and controlling crystallization processes using advanced control strategies.

In this context, the increasing adoption of Quality by Control (QbC) principles, as opposed to the more traditional Quality by Design (QbD) approach based on design of experiments, has become essential. QbC emphasizes real-time control and adjustments, allowing for more consistent product quality, especially when integrated with advanced control strategies and model-based methods. This shift has resulted in more robust and flexible crystallization processes across multiple industries. The implementation of QbC has transformed crystallization control by transitioning from reactive control strategies to proactive, real-time

* Corresponding author at: Instituto de Química, Rio de Janeiro State University (UERJ), Rua São Francisco Xavier, 524, Maracanã, Rio de Janeiro, RJ, 20550-900, Brazil.
E-mail address: marcellus@peq.coppe.ufrj.br (M.G.F. de Moraes).

https://doi.org/10.1016/j.dche.2024.100208
Received 22 September 2024; Received in revised form 4 December 2024; Accepted 5 December 2024
Available online 18 December 2024

Table 1
Overview of studies using ML for modeling and controlling crystallization processes.

Methodological aspect	Publications
Pure ML models	Guardani et al. (2001), Vasanth Kumar et al. (2008), Heisel et al. (2018), Heisel et al. (2019), Manee et al. (2019), Ma et al. (2020), Sirohi et al. (2020), Lima et al. (2022a), Zheng et al. (2022a,b), An et al. (2022), Lima et al. (2022b), Gan et al. (2022), Lima et al. (2023a), Moraes et al. (2023), Sitapure and Kwon (2023b), Sitapure and Kwon (2023a) and Nyande et al. (2024)
Hybrid models	Lauret et al. (2001), Georgieva et al. (2003), Galvanauskas et al. (2006), Oliveira et al. (2009), Lima et al. (2023b), Sitapure and Kwon (2023c) and Wu et al. (2023a)
ML Control	Rohani et al. (1999), Duan and Li (2015), Li and Duan (2015), Kittisupakorn et al. (2017), Daosud et al. (2017), Szilagyi and Nagy (2019), Oner et al. (2020) Nielsen et al. (2020), Lima et al. (2022a), Wang et al. (2022), Zheng and Wu (2022b) Zheng et al. (2022b,a), Lima et al. (2022b), Wu and Wu (2023), Wu et al. (2023a), Lima et al. (2023a), Moraes et al. (2023), Sitapure and Kwon (2024), Meyer et al. (2024), Sitapure and Kwon (2024), Lima et al. (2024a,c) and Jong et al. (2024)
Reinforcement learning	Zhang et al. (2020), Manee et al. (2021), Benyahia et al. (2021a), Benyahia et al. (2021b), Manee et al. (2022), Anandan et al. (2022), and Meng et al. (2023)

frameworks (Szilagyi and Nagy, 2019; Szilágyi et al., 2022). These advancements are particularly critical in pharmaceutical manufacturing, where tight regulation of product quality is necessary to ensure safety and compliance with industry standards.

In their classic review about the advances and perspectives of crystallization control, Nagy and Braatz (2012) described the recent advancements at the time in crystallization control by the improvement of real-time sensor technologies and pharmaceutical industry needs, focusing on accurate measurement and robust control of crystal characteristics. Promising research directions highlighted by the authors then included model-free control methods, innovative crystallizer designs, simultaneous control of crystal properties, and interconnected systems for multicomponent crystallization, aiming to enhance process consistency and control. It is worth noting that, at that point, the exploration and use of machine learning (ML) techniques for the control of crystallization processes were not considered promising nor of significant prominence.

Over the past decade, ML advancements have been driven by increased computational power, the availability of extensive experimental data, and more efficient algorithms. ML techniques have made remarkable progress in analyzing and predicting complex behaviors from large datasets, evident in applications like web searches, email filtering, and image recognition (Xiouras et al., 2022). In crystallization, ML is emerging as a promising tool for predicting and optimizing processes with respect to product specifications (Szilagyi and Nagy, 2019; Zheng et al., 2022a).

From the point of view of predictive modeling and model-based control strategies, classic first-principles modeling based on fundamental physics and chemistry principles have been mainly used. These models describe crystallization processes using equations governing molecular interactions, thermodynamics, and kinetics, including nucleation theory, crystal growth models, and phase diagrams (Fujiwara et al., 2005; Morris et al., 2015; Temmel et al., 2018; Quilló et al., 2021; Moraes et al., 2023). While these models offer deep insights, they often require extensive computational resources and detailed system knowledge. They can struggle with the complexity and scale of industrial processes, especially with high-dimensional or noisy data (Eisenschmidt et al., 2016).

In this way, ML integration into crystallization modeling and control offers several advantages over traditional methods (Sharma and Liu, 2022). ML excels in handling vast and complex datasets with high-dimensional characteristics. These techniques applied to pharmaceutically relevant crystalline materials (Devogelaer et al., 2021) and crystallization processes can analyze extensive datasets from real-time monitoring technologies like process analytical technologies (PATs) (Ma et al., 2020). These models provide insights into both solution and solid-state properties, enabling real-time simulation and control of complex nonlinear dynamics (Nyande et al., 2024). By linking key quality attributes of crystalline products with adjustable process parameters, ML aids in optimizing processes and enhancing crystal product quality (Lee, 2014; Heng et al., 2021).

ML has become an important asset in the field of crystallization, offering novel methods to use data in tackling long-standing issues such as efficient monitoring, modeling, controlling, and accurately predicting the physical and physicochemical properties of crystalline materials (Meyer et al., 2024; Szilagyi and Nagy, 2019). The adaptability of ML models reduces reliance on trial-and-error methods and empirical adjustments, streamlining process development and enhancing efficiency. ML-driven adaptive control systems fine-tune parameters automatically, responding to process variations with precision. ML models can integrate various data sources, including historical process data, real-time monitoring results, and theoretical predictions (Sitapure and Kwon, 2023a). Real-time data analytics and ML-driven control systems are becoming more autonomous and precise, aided by advancements in sensor technologies and predictive algorithms (Sitapure and Kwon, 2023b; Wu and Wu, 2023). Even with this advantages, ML approaches present some negative points, such as the necessity of big datasets. Moreover, ML models that not consider physical laws in their formulation are empirical and cannot be applied outside of the training conditions.

Emphatically, the increasing importance of applying ML to crystallization in recent years is highlighted in the two recent reviews by Xiouras et al. (2022) and Lu et al. (2024). Both reviews have a broader focus regarding the main applications where ML would be employed, in the context of the product (crystalline materials) and the process. Xiouras et al. (2022) provided a more holistic perspective on the application of ML to crystallization as a whole. Specifically, regarding the topic of crystallization process modeling and control, they highlight the classic contribution of model-free data-driven models for supersaturation control, concentration control, and direct nucleation control. The applications of ANN is cited as the most prominent, and some of the early studies using ANN in the context of NMPC were presented. Lu et al. (2024) emphasized the use of ML for investigating crystal structures and elucidating physicochemical properties from structure prediction models. The authors presented a historical evolution, highlighting the acceleration of crystal structure prediction by machine learning techniques, as well as their use for predicting important properties such as solubility, melting point, and crystal habit. In a second phase, the review focused on the use of ML in optimization and control of crystallization processes.

The empirical models based on ML are typically quick to develop and computationally efficient. Even though they can capture relationships in data, they lack physical interpretation, require large datasets and should not be used for extrapolation. In this way, the so-called hybrid models can combine the strengths of interpretability and generalization of phenomenological models with the adaptability of the empirical ones. Regarding hybrid models, Xiouras et al. (2022) and Lu et al. (2024) point to their potential contribution by describing, respectively, the works of Georgieva et al. (2003), who used artificial neural networks for modeling the kinetics of growth, nucleation, and agglomeration of sugar crystallization, and Wu et al. (2023a), who developed physics-informed recurrent neural network models for open-loop and closed-loop predictions for aspirin crystallization. However, a more detailed presentation and discussion on hybrid modeling for crystallization processes were not within their scopes.

Overall, both reviews provided a detailed review of ML applications for utilizing information from PATs and sensing technologies, as well as for predicting and classifying physicochemical properties of crystalline materials of interest. Thus, more emphasis is placed here on process monitoring, crystal structure investigation, and material or system characterization, such as solubility information.

The present paper provides an in-depth examination of process modeling and advanced control aspects of ML and phenomenological-ML hybrid approaches, highlighting their potential as a promising tool for crystallization processes. From a Process Systems Engineering (PSE) perspective, it offers an up-to-date guide, presenting key ML methodologies and also pointing to applications that bridge physics-based and data-based tools. Table 1 provides an introductory overview of the paper's scope by showing the applications of ML for modeling and advanced control of crystallization process. They are subdivided in studies using pure ML models, hybrid models, control, and reinforcement learning.

In this way, this overview provide a critical review and evaluation based on the ML methods in which significant progress has been verified in recent years. For the ML-modeling of crystallization processes, the following methods are presented in terms of their conception and discussion in the recent literature: (a) neural network models (Section 2.1), (b) hybrid models (Section 2.2); (c) symbolic regression models (Section 2.3). In Section 3, the machine learning-based control strategies (Section 3.1) and reinforcement learning control approaches (Section 3.2) are discussed. In Section 4, future perspectives and challenges regarding the use of ML in practical crystallization are emphasized.

2. Machine learning for modeling crystallization processes

2.1. Models based on neural networks

Artificial neural networks (ANNs) are a mathematical representation designed to imitate the interconnected systems of neurons in the human brain. The primary objective of a neural network is to capture the connections between a given set of input and output patterns (Abdi-Khanghah et al., 2018). This entails the network initially learning from historical instances, wherein pairs of input and output data are established for a specific system referred to as the training set. Consequently, the network's capability to predict new outputs is exercised by employing novel input sets (McBride and Sundmacher, 2019).

The conventional configuration of a neural network, as depicted in Fig. 1, encompasses three main parts: the input layer, one or more hidden layers, and the output layer (Kumar et al., 2013). Initially, external information is received in the input layer, which then transmits it to the hidden layer. Within the hidden layer, information processing takes place. Subsequently, the output layer receives the processed information and conveys the outcomes to an external recipient (Golhani et al., 2018). This kind of ANN is also known as feedfoward network which means that an information that enters the network always passes

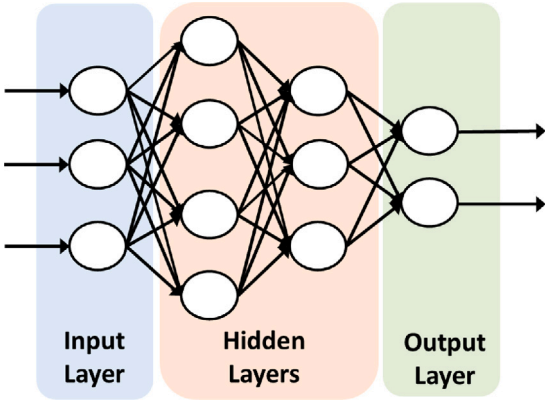

Fig. 1. Typical structure of a feedforward neural network.

to the next layer, never returning to the previous layer. Multilayer perceptron (MLP) network is an example of a feedforward network applied in the literature and presents the same structure of Fig. 1 (Ojha et al., 2017).

Another kind of feedforward network is known as radial basis function (RBF) neural network. This ANN is composed of three layers: one input layer, a single hidden layer and an output layer (Kurban and Beşdok, 2009). The distinguishing feature of the RBF network lies in its hidden layer, where every node denotes a data cluster centered at a specific point with an assigned radius. Each node within this layer computes the distance between the input vector and its own center (Pham et al., 2020). This computed distance undergoes transformation through a chosen basis function, and the outcome is then outputted from the node (Yu et al., 2008).

The essential aspect of training a neural network involves determining the weight and bias parameters. An approach commonly employed for achieving this in a feedforward network is known as backpropagation. The primary objective during training is to minimize the disparity between the anticipated and desired outcomes. Within the backpropagation technique, the computed error in the output layer is backpropagated to the preceding layer, enabling the refinement of weights and biases within that layer. Consequently, the initial phase involves fine-tuning the weights and biases between the output and hidden layers, followed by making corresponding adjustments within the input and hidden layers. One technique employed for executing this modification is the gradient descent method (Baughman and Liu, 2014).

The first use of neural networks for crystallization processes was developed by Woinaroschy et al. (1994). They used MLP networks to predict the crystal size distribution (CSD) for the crystallization of $CaCO_3$ from aqueous solution in a mixed-suspension mixed-product removal (MSMPR) crystallizer. Then, this model was used for an optimization problem that consisted of finding the operating parameters, which led to the desired mean crystal size dimension and dispersion. After that, there was an increase in the number of publications using neural networks for modeling crystallization processes. Fig. 2 presents the annual number of publications in the chemical engineering field for modeling crystallization processes using neural networks from 1994 to 2024 (Elsevier, 2024). Fig. 2 presents a large growth in the number of articles using this approach for modeling crystallization processes in the last five years.

The following examples reflect the diversity of applications of feedforward neural networks over the years. Guardani et al. (2001) used feedforward networks for modeling sodium chloride crystallization in a solution containing water and ethanol. The ML model was able to successfully predict the CSD in this system. Vasanth Kumar et al. (2008) created MLP networks that effectively predicted the crystal

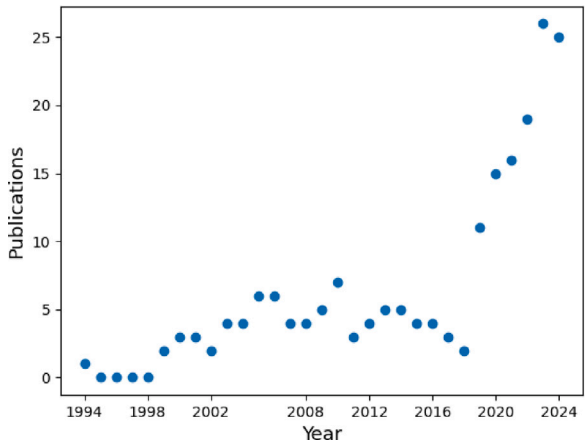

Fig. 2. Number of publications per year in the chemical engineering field using neural networks for modeling crystallization processes from 1994 to 2024 (Elsevier, 2024). Keywords: crystallization and "neural network" and (model or modeling), limited to engineering and chemical engineering fields.

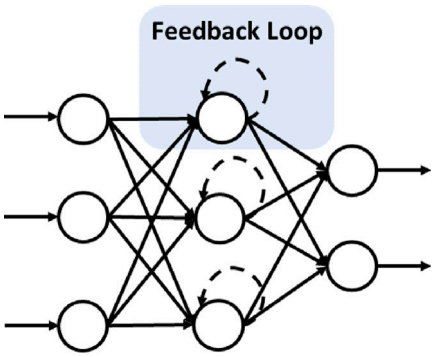

Fig. 3. Structure of a recurrent neural network.

growth rate of sucrose. When comparing the data-driven model to the traditional approach of finding an empirical expression that correlates the crystal growth rate with the operating variables studied, the neural network demonstrated superior performance. Ma et al. (2020) introduced three semiempirical models and neural networks to estimate the metastable zone widths for the reactive crystallization of lithium carbonate. These models were created solely from experimental data, and the neural networks were able to predict this characteristic with high accuracy. Lima et al. (2023a) used MLP networks to predict the solution concentration and the first four moments of the CSD for the potassium sulfate crystallization, considering nucleation, crystal growth and dissolution.

Computational advances allowed the development of new structures of ANNs, such as feedback networks. This kind of ANN presents a hidden state along with a feedback loop of hidden states (Ren and Ni, 2020). Through this feedback loop, past information is incorporated into the current state, facilitating the update of the hidden state (Shahnazari, 2020). This kind of structure gives the network the capability to simulate time series and capture the dynamic behavior (Petsagkourakis et al., 2020). Feedback networks are also known as recurrent neural networks. The structure is presented in Fig. 3.

The incorporation of temporal dependencies in neural networks necessitates the adoption of a distinct algorithm for computing gradient updates of model parameters to minimize the loss function, known as backpropagation through time (BPTT). Initially, this approach computes the discrepancy between target and output values and retains it for each past time step. Subsequently, the updates to weight gradients are computed as the network receives feedback (Shahnazari, 2020). Nevertheless, RNNs trained using this method may encounter challenges like vanishing or exploding gradients (Lillicrap and Santoro, 2019), prompting the need for enhancing this algorithm and devising new RNN architectures such as long short-term memory (LSTM) networks, gated recurrent unit (GRU), and echo state networks (ESNs) (Ren and Ni, 2020).

Fig. 4 presents the structure of three kinds of RNNs. The GRU is characterized by its different structure of hidden layer, which is showed in Fig. 4a. The hidden layer of this network consists of units referred to as cells, which undergo updates based on internal information. These units are constituted of gates that govern the inclusion or removal of information from the cell. The GRU network comprises two gates: the update gate and the reset gate (Chen et al., 2023; Hong et al., 2023). The primary function of the update gate is to determine the extent to which information from the previous state is transferred to the current state. Conversely, the reset gate is tasked with determining the extent to which information from the previous state should be disregarded (Wu et al., 2023b).

LSTM is an alternative to conventional RNNs that addresses issues like gradient vanishing and explosion. Unlike the GRU network, LSTM employs a similar cell structure but features three gates instead of two, as depicted in Fig. 4b. Consequently, the LSTM presents a more complex structure and comprises more parameters than the GRU (Liao et al., 2022). The initial gate, known as the forget gate, determines which information from the previous cell state should be discarded for updating the current state (Inapakurthi et al., 2021). Additionally, the input gate selects pertinent information to modify the cell state, while the output gate regulates information passage to the subsequent hidden state via the sigmoid function (Elsheikh et al., 2021).

The third approach of RNN presented in Fig. 4c is the ESN. Unlike the previous approach, this kind of network does not present a neuron with a cell structure and memory. The ESN is composed of an input layer, a dynamical reservoir, and an output layer (Dias et al., 2019). The reservoir layer is the recurrent part, where the outputs of the reservoir and output layers are fed back (Matino et al., 2019). The weights from the reservoir layer are randomly determined by a normal distribution and rescaled for the resulting system to be stable but still demonstrate rich dynamics. As a result, the only step in training ESN is finding the weight values of the output layer, which is usually done by linear regression (Antonelo et al., 2017; Bo and Zhang, 2018).

The use of RNNs for modeling crystallization processes is recently growing in the literature, which is reflected in Fig. 2. Lima et al. (2022b) trained MLP, ESN and LSTM networks to predict the solute concentration in the potassium sulfate batch crystallization. Zheng et al. (2022b) and Zheng et al. (2022a) used a basic RNN model to describe the seeded fesoterodine fumarate cooling crystallization and dissolution in a batch reactor. They used the RNN to predict the solute concentration, temperature of the reactor, and the number of crystals. Lima et al. (2022a) and Moraes et al. (2023) used ESN to model the nucleation and crystal growth in the potassium sulfate batch crystallization process. They used this network to predict the first four moments of the CSD and the solute concentration. An et al. (2022) used GRU and LSTM networks to predict the magma density in a maleic acid continuous crystallization process.

There is also a specific kind of deep neural network used to develop models based on images known as convolutional neural network (CNN). A CNN is usually composed of three kinds of layers: convolutional, pooling and fully-connected layer (Sirohi et al., 2020). The hidden layer is composed of pooling layers and convolutional layers. The pooling layers are used to reduce the size of the outputs of the convolutional layers, which reduces the number of calculated parameters (LeCun et al., 2015).

CNNs are usually used to modeling crystallization by acquiring images of the crystal and predicting some characteristics of the system from this information. One example of this kind of application is

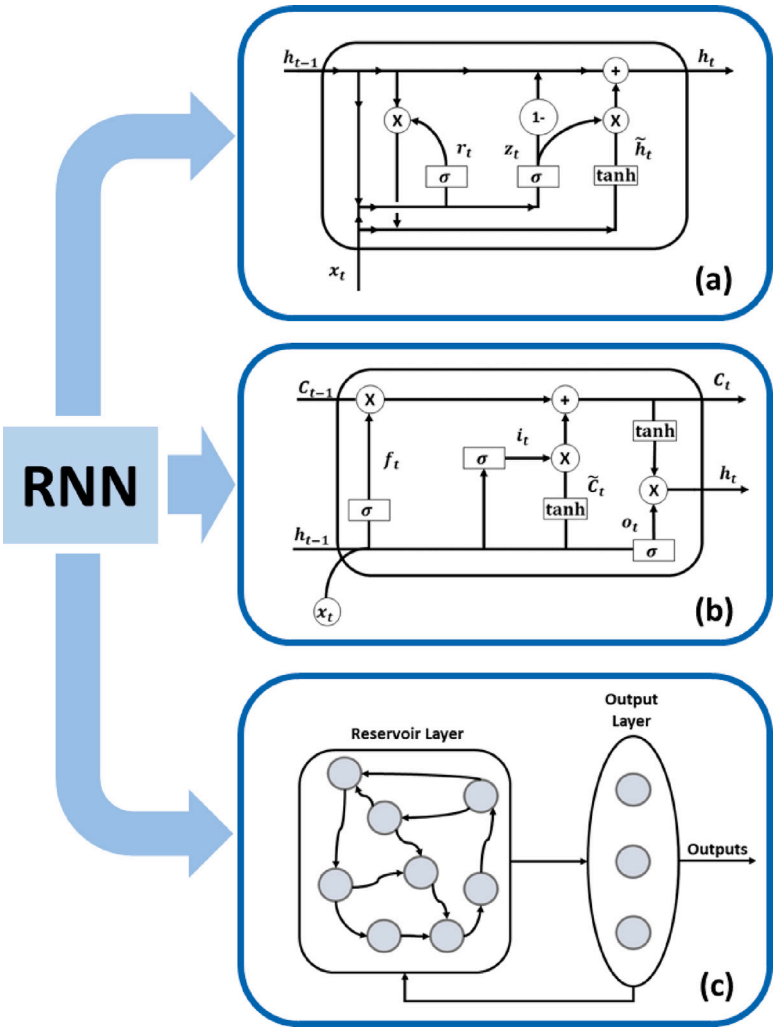

Fig. 4. Different architectures of RNNs, in which (a) presents the gated recurrent unit, (b) long short-term memory, and (c) illustrates the echo state network.

the work of Wang et al. (2022), in which the authors use CNN to predict the CSD based on the images of the crystallization process. The predictions of the CNNs were used as inputs of an RBF network that was applied to model a batch cooling crystallization process. There are other applications of CNNs using the images of the crystallization process to predict the CSD (Manee et al., 2019; Gan et al., 2022). CNNs were also used to measure the agglomeration for the crystallization of adipic acid in water (Heisel et al., 2018, 2019). Salami et al. (2021) used CNN to detect contamination in the reactive crystallization of cephalexin with phenylglycine.

Transformer algorithms are another kind of neural network introduced by Vaswani et al. (2017). The transformer architecture is a neural network model designed for sequence-to-sequence translation, typically used to convert an input sequence into an output sequence. Therefore, it consists of an encoder stack and a decoder stack (Vogel et al., 2023). The encoder transforms a sequence of input tokens into a numerical representation suitable for further processing within the model. It captures the meaning of each token in the sequence (Mann and Venkatasubramanian, 2021). This numerical representation is then passed to the decoder stack, which translates it back into a sequence of output tokens in the target language. The translation process generates tokens one by one, with the decoder using both the encoder's numerical output and previously generated tokens to determine the probabilities for the next token in the sequence (Deihim et al., 2023). Different from RNNs, transformer algorithms do not use recurrence but processes the entire sequence at once, allowing more parallelization (Vogel et al., 2023).

Modeling crystallization processes using transformer algorithms was a topic considered in recent researches. Initially, Sitapure and Kwon (2023b) proposed a time-series-transformer (TST) algorithm and used to model crystallization of dextrose. Their methodology was able to successfully model the nucleation and growth of dextrose crystals. Then, Sitapure and Kwon (2023a) proposed a TST for modeling different crystallization processes. To develop their model, they considered data from nucleation and growth for crystallization of dextrose, sucrose, and lactose, developing 20 systems. Their proposal could effectively model these crystallization processes and successfully predict a crystallization system not considered in the training set.

There are different kinds of neural network architectures, and the selection of which one to model a crystallization process is an important topic. Lima et al. (2022b) and Lima et al. (2022a) compared the performance of MLP, ESN and LSTM networks for predicting the concentration and the first four moments of the CSD, respectively, for the potassium sulfate batch crystallization process. In both works, the neural networks were tested to make predictions one to five sampling times ahead. These neural networks were trained using simulated and experimental data and tested with a dataset composed of nine experimental and three simulated batches. The performance of the neural networks developed by Lima et al. (2022b) is presented in Fig. 5. In both works, all neural networks efficiently predicted the variables one sampling time ahead. However, the performance of the ANNs was worse for predicting multiple sampling times forward, specially the LSTM. The ESN presented the best performance in these works

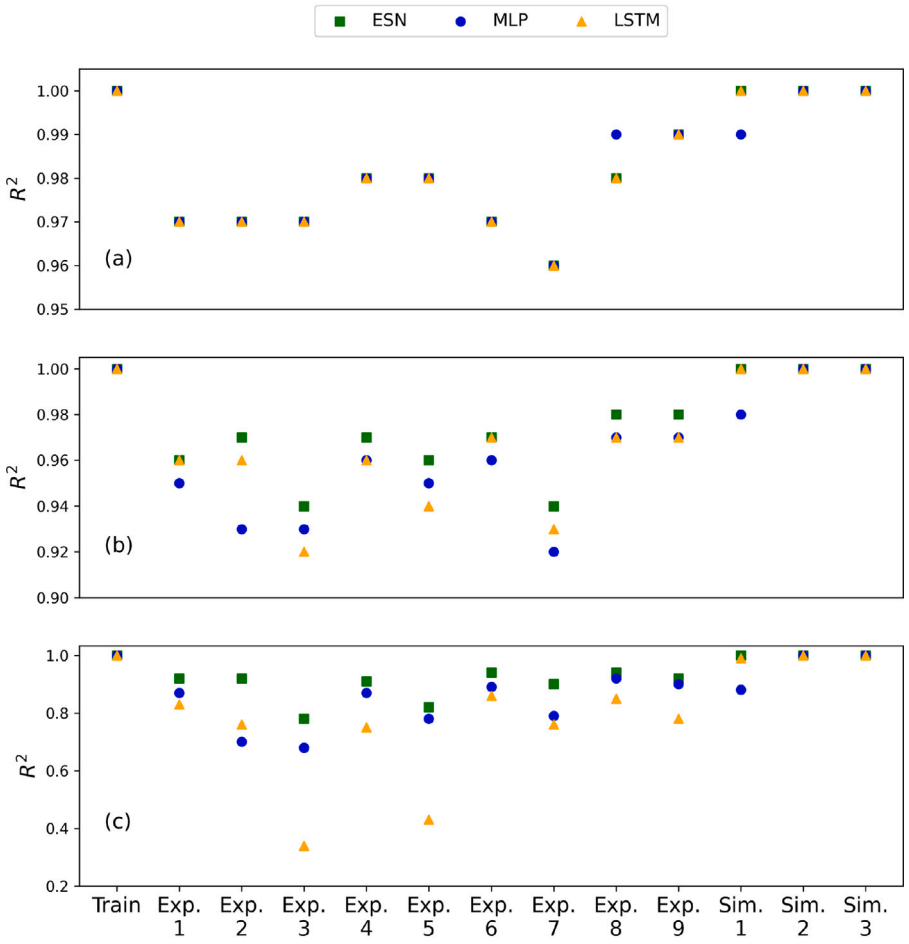

Fig. 5. Performance of the neural networks developed by Lima et al. (2022b).
Source: Adapted from Lima et al. (2022b).

and was the most suitable for modeling the potassium sulfate batch crystallization process.

It would be expected for the LSTM network be the best choice for modeling a crystallization process as it presents a structure which accounts for previous inputs with a memory. However, this did not happen in the studies developed by Lima et al. (2022a) and Lima et al. (2022b). This behavior was also demonstrated by Li and Qin (2023), in which they compared the performance of the LSTM with partial least squares (PLS), Lasso, and support vector regression (SVR) on an industrial 660 MW boiler process, an industrial debutanizer process, and two simulation cases of a nonlinear reactor. They demonstrated that the LSTM presented worse prediction accuracy compared to all other approaches. Therefore, the selection of the appropriate ANN to model a crystallization process depends on which architecture demonstrates the best performance, requiring testing of different configurations to determine this.

Even with all these applications of neural networks for modeling crystallization processes, this is still an emerging field and there are some topics that still need to be explored (Xiouras et al., 2022). Lima et al. (2024b) presented the relevance of making a proper statistical analysis of the model and study the model's uncertainty. This issue was not taken into account in most works proposing neural network models for crystallization processes. One methodology applied in the literature to study the uncertainty of neural network models is based on the Monte Carlo uncertainties training strategy. The process begins by applying the Markov Chain Monte Carlo method to estimate the uncertainty in the non-linear model parameters that represent the system (Costa et al., 2022). Following this approach, the validated model is used to generate synthetic data, which then serve as the basis for constructing neural networks in two phases. The first phase involves defining the neural network type and its overall architecture, followed by hyperparameter optimization. Once the optimal network architecture is identified, the second phase entails conducting Monte Carlo simulation training to propagate the uncertainty from the non-linear model into the AI model (Costa et al., 2023). The final step of the proposed methodology involves validating and assessing the uncertainty of the trained model. This methodology was applied for some chemical processes, such as pressure swing adsorption (Costa et al., 2022), polymerization (Costa et al., 2023) and a submersible pump system (Costa et al., 2024). Therefore, the application of this methodology for analyzing the uncertainty of the neural network parameters used for modeling crystallization processes is a relevant topic for future studies.

2.2. Hybrid models

A hybrid model is a combination of data-driven and first principles models (Sharma and Liu, 2022). This methodology blends the adaptability of data-driven techniques with the insights provided by physical laws from first principles models (Zendehboudi et al., 2018). Hybrid models can be extrapolated, different from ANNs that are empirical models and can only be used for the conditions of the training dataset (McBride and Sundmacher, 2019). Lima et al. (2023b) compared a hybrid model, single ANNs, and a population balance model for potassium sulfate batch crystallization. The hybrid model used ANNs to predict growth, nucleation, and dissolution rates, as well as concentration and CSD moments under various conditions. For modeling

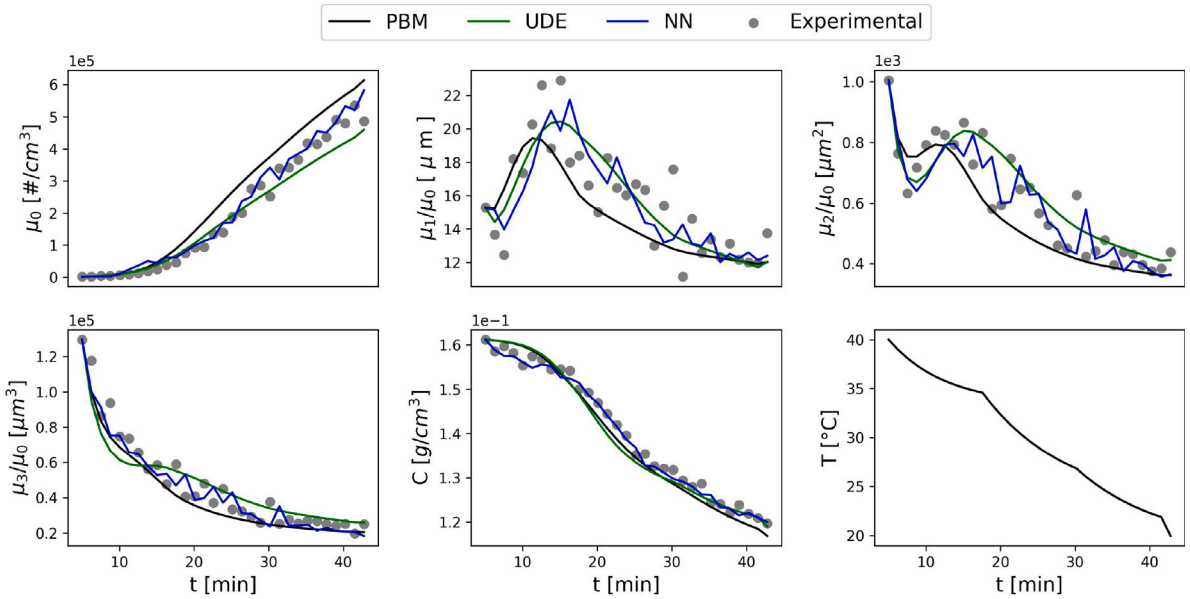

Fig. 6. Comparison between the ANNs, the population balance model, and the hybrid model to predict one batch under the supersaturated condition of the test dataset. *Source:* Adapted from Lima et al. (2023b).

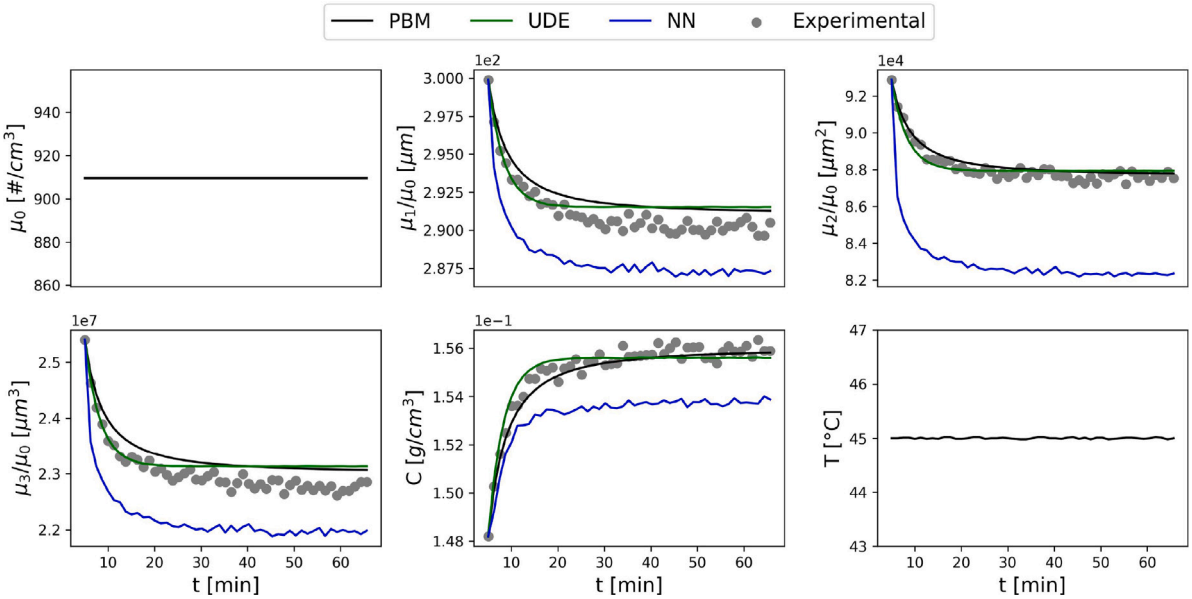

Fig. 7. Comparison between the ANNs, the population balance model, and the hybrid model to predict one batch under dissolution condition of the test dataset. *Source:* Adapted from Lima et al. (2023b).

nucleation and growth, the hybrid model showed performance similar to the population balance model, as presented in Fig. 6. However, the ANN struggled with dissolution modeling due to the small dataset, as shown in Fig. 7. Wu et al. (2023a) also noted that hybrid models require smaller training sets than standalone ANNs.

For modeling crystallization processes, hybrid models are usually a combination of neural networks and population balance models. Therefore, these works are included in the publications in Fig. 2. Different hybrid approaches were used in the literature to model crystallization processes. Universal differential equations (UDEs) are one of these methodologies, which consist of differential equations augmented with one or more universal approximators (Hornik et al., 1989). Numerous functions and series have been identified as universal approximators because of their flexibility and adaptability. ANNs are particularly effective in higher dimensions as universal approximators. Their layered structure and use of nonlinear activation functions enable them to accurately approximate functions in multidimensional spaces. ANNs are well-suited for high-dimensional approximation tasks due to their capacity to adapt, learn from data, and generalize (Lima et al., 2023b). Fig. 8 shows an example of a UDE using ANN as its universal approximator.

For crystallization processes, ANN are usually used as the universal approximator for modeling crystallization processes. The strategy consists of replacing the rate equations by ANNs and use the predictions of the population balance equations to calculate the loss function. This approach was initially used by Lauret et al. (2001) for modeling the crystal growth in sucrose crystallization. They replaced the growth rate equation by an ANN and considered the difference in the experimental and calculated solution concentration as the loss function. Then, this approach was enhanced and used for modeling

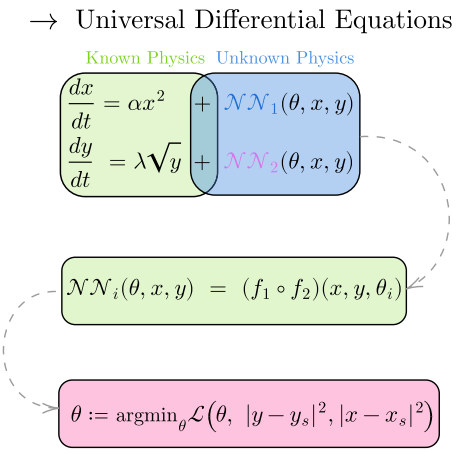

Fig. 8. Illustration of UDE approach for a dynamic system.

the batch crystallization of sugar accounting for nucleation, growth and agglomeration (Georgieva et al., 2003; Galvanauskas et al., 2006; Oliveira et al., 2009). To calculate the loss function, they considered the difference between the calculated and the predicted mass of crystals.

Recently, Lima et al. (2023b) proposed a hybrid model for the potassium sulfate batch crystallization. They used ANNs to obtain the nucleation, growth and dissolution rates, and considered the solute concentration and the first four moments of the CSD to calculate the loss function. The methodology proposed by Lima et al. (2023b) also presented the advantage of not needing a solubility model to calculate the nucleation, dissolution and growth rates, as the ANN inputs were temperature, solute concentration, zero-order moment and mean crystal volume. Sitapure and Kwon (2023c) proposed another hybrid modeling approach combining TSTs to population balance model. They used TSTs to obtain the nucleation and growth rates for the batch crystallization of dextrose. Then, the calculate rates were used in the population balance equations to obtain the CSD.

Another hybrid approach used to model crystallization processes is the physics-informed neural networks (PINNs). This approach also combines the physical knowledge of the differential equations to the ANN training but in a different way that is done by UDE. In the PINN methodology, the neural network is trained to fit the data and to ensure that its predictions satisfy the differential equations governing the system (Cai et al., 2021). Therefore, the differential equations are used as constraints during the training step (Santana et al., 2022). This methodology is presented in Fig. 9. Recently, Wu et al. (2023a) proposed the first application of PINNs for modeling a crystallization process. They developed a physics-informed recurrent neural network (PIRNN) designed for modeling the crystallization process of aspirin. The model was trained with simulated data and incorporated nucleation and crystal growth mechanisms.

Regarding the different hybrid modeling approaches, their goal and advantages are similar. Their difference is related to the way the training is developed. PINNs directly incorporate the physics of a problem by embedding differential equations into the neural network's loss function, making them particularly effective for solving partial or ordinary differential equations with known governing laws (Zhang et al., 2024). However, they can face challenges in training, especially for high-dimensional or stiff problems, and require careful network design. On the other hand, UDEs offer a more general framework, allowing for a broader range of differential equations to be solved, including nonlinear and non-local ones (Rackauckas et al., 2020). UDEs seamlessly blend data and physics, providing a more flexible approach to modeling, but they can be more complex to implement and require a deep understanding of the system dynamics (Nogueira et al., 2022). While both methods allow for grid-free solutions and can handle noisy or sparse data, UDEs tend to provide better interpretability and scalability for diverse and more complicated problems, whereas PINNs excel when the governing equations are well-defined and directly available (Rackauckas et al., 2020). The choice between PINNs and UDEs depends on the complexity of the problem, the data available, and the specific nature of the differential equations one are dealing with Silvestri et al. (2023). If a more flexible and general approach is needed, UDEs might be better. However, when specific physics models are available and the goal is to directly incorporate them into the learning process, PINNs might be more suitable.

The application of hybrid models for crystallization processes is an emerging field that has many opportunities of research. As previously presented, hybrid models for crystallization processes are usually a combination of population balance equations with ML models to describe the rates, such as nucleation and crystal growth. This kind of application brings advantages. The crystallization rates are functions of supersaturation, which are described in different ways in the literature. Kim et al. (2023) described the supersaturation as the ratio between the concentration and the equilibrium concentration to develop their population balance model for paracetamol crystallization. On the other hand, Moraes et al. (2023) considered the difference between these concentrations to model the supersaturation in their model for potassium sulfate crystallization. Moreover, Szilágyi et al. (2022) divided the difference between the solute concentration and the equilibrium concentration by the equilibrium concentration to model supersaturation. Therefore, there is a trial-and-error methodology in the literature to find the most suitable way to model a specific crystallization process using the conventional phenomenological approach.

Hybrid models avoid this difficulty of finding the most suitable expression for describing the rates in crystallization process. The biggest effort regarding hybrid models is selecting the hyperparameters of the ML learning model, which is more simple than finding the most suitable rate equation to describe the process. Lima et al. (2023b) were able to model the nucleation, crystal growth and dissolution rates only using temperature, concentration, and the zero and third-order moments as inputs. Therefore, they did not need to develop a model for calculating the solubility to obtain these rates. For crystallization of a solute in a single solvent, solubility may be simple to model as it is only a function of temperature (Worlitschek and Mazzotti, 2004; Li et al., 2017; Griffin et al., 2017). However, this is not the case for crystallization with addition of antisolvent. This is a ternary system, with solubility dependent on temperature and the solvent/antisolvent composition (O'Ciardhá et al., 2012; Assis et al., 2021). In these cases, the solubility presents a significant nonlinearity, which can be a challenge to model (Nagy et al., 2008a). Therefore, hybrid approaches can be an efficient tool for modeling crystallization with antisolvent addition and avoid solubility model.

Some hybrid approaches were applied only a single time for modeling crystallization processes (Wu et al., 2023a; Sitapure and Kwon, 2023c). Furthermore, hybrid models were applied for only few crystallization systems, in which most of them used this methodology for sugar crystallization (Lauret et al., 2001; Georgieva et al., 2003; Galvanauskas et al., 2006; Oliveira et al., 2009; Sitapure and Kwon, 2023c). There are not many applications of hybrid models for the crystallization of pharmaceutical compounds (Wu et al., 2023a). More than 90% of active ingredients produced in the pharmaceutical field are crystals (Tang et al., 2021), being a relevant field to be considered in future studies. Moreover, the studies proposing hybrid models for crystallization processes do not account for an analysis of the model's uncertainty. This is also a relevant topic to be considered in future studies.

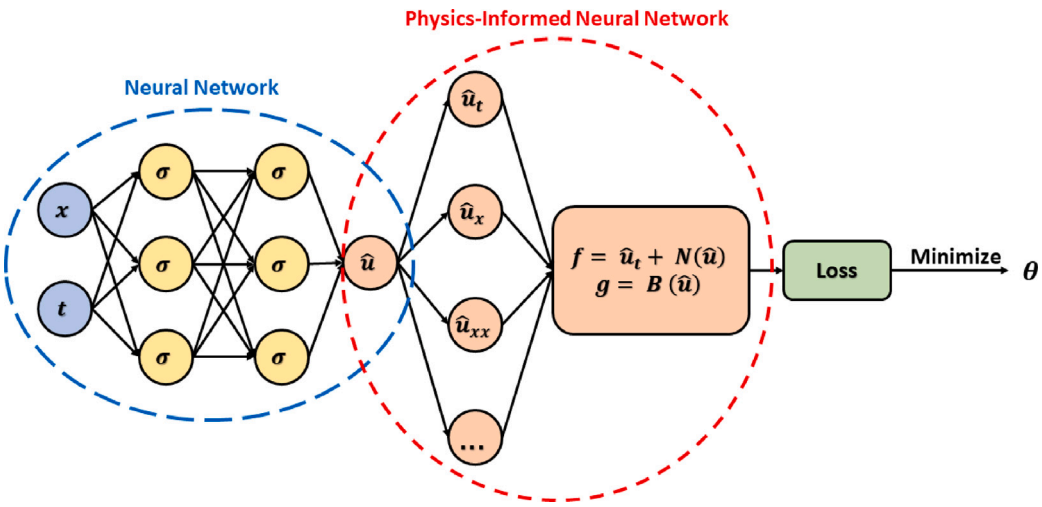

Fig. 9. Physics-informed neural networks methodology.

2.3. Symbolic regression

A novel data-driven approach that was used for modeling chemical processes is symbolic regression (Narayanan et al., 2022; Scheffold et al., 2021). In a symbolic regression problem, a set of mathematical expressions is created using fundamental elements such as mathematical operators and state variables (Cohen et al., 2023). The goal of symbolic regression is to explore this set to find the most effective expression by leveraging these basic components. Therefore, the optimization challenge in symbolic regression is to determine the optimal structure and parameters for the model (Wang et al., 2019). The objective function considered in this optimization problem is to minimize the error between the measured values and the values predicted by the model.

Symbolic regression problems are usually solved using the genetic programming (GP) algorithm, which is a particular kind of genetic algorithms (GAs). In Genetic Programming (GP), solutions are represented as tree-like structures known as chromosomes, which consist of nodes and branches (Wang et al., 2019). For example, Fig. 10 shows a tree-structured chromosome that models the mathematical function $X_1 + \cos(0.5X_0)$. This tree features interior nodes for mathematical operations such as sum, cosine, exponential and logarithm, as well as terminal nodes for variables and constants.

The Genetic Programming (GP) algorithm starts by generating trees with randomly chosen terminal nodes and mathematical functions,

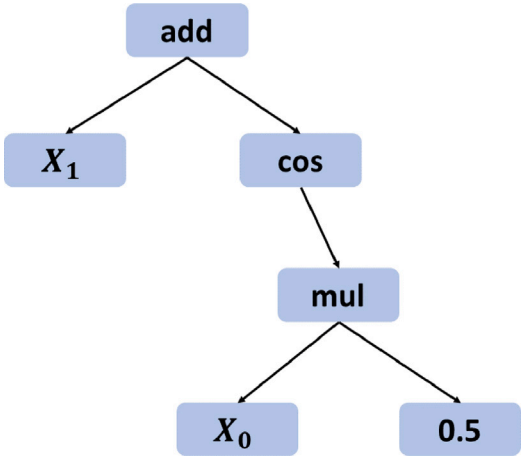

Fig. 10. GP tree-structured chromosome for the mathematical function $X_1+\cos(0.5X_0)$.

varying in size and structure. The mathematical operations and variables used in symbolic regression are defined by the user (Cranmer, 2023). The performance of these initial trees is evaluated by comparing their predictions to actual values using an error metric, such as mean absolute error (MAE) and mean squared error (MSE) (Kay et al., 2023). The algorithm then progresses by applying genetic operations like crossover and mutation. Initially, individuals are selected as parents based on their error values, with those having lower errors being more likely to be chosen. During crossover, two parent trees are combined to produce offspring by replacing a random subtree from one parent with a random subtree from the other. This process is demonstrated in Fig. 11, where a segment of tree B is inserted into tree A to create tree C.

During the mutation operation, a single individual is selected as the parent, and a subtree within this parent is randomly replaced with a newly generated structure. This procedure is illustrated in Fig. 11, where a subtree of tree A is replaced to create tree D. Mutation operations are carried out iteratively until either the error value falls within predefined criteria or the maximum number of generations is reached (Wang et al., 2019).

Another kind of symbolic regression used for modeling chemical processes is the sparse identification of nonlinear dynamics (SINDy). SINDy is particularly used for discovering the governing equations of dynamical systems (Brunton et al., 2016). Moreover, it uses a predefined library of functions and emphasizes sparsity in the regression process to find the simplest model that describes the dynamics (Fukami et al., 2021). Recently, Nyande et al. (2024) first applied symbolic regression for modeling crystallization processes using the SINDy methodology. They used this approach to identify the dynamics of three crystallization systems: MSMPR crystallizer, protein lysozyme in a batch stirred tank crystallizer, and cooling crystallization of paracetamol. The SINDy approach was able to find the models to effectively describe these systems.

Compared to a black-box ML models, symbolic regression presents the advantage of obtaining models with interpretability (Wang et al., 2019). To apply a hybrid approach for modeling a crystallization process, a prior knowledge of the studied system is necessary (Lima et al., 2023b). On the other hand, the use of symbolic regression does not need this information to obtain an interpretable model. Moreover, hybrid models still contain an uninterpretable component, whereas symbolic regression does not. Zendehboudi et al. (2018). However, the model obtained by symbolic regression is interpretable but does not necessarily follow the physical laws and may be empirical, which is different from a hybrid model.

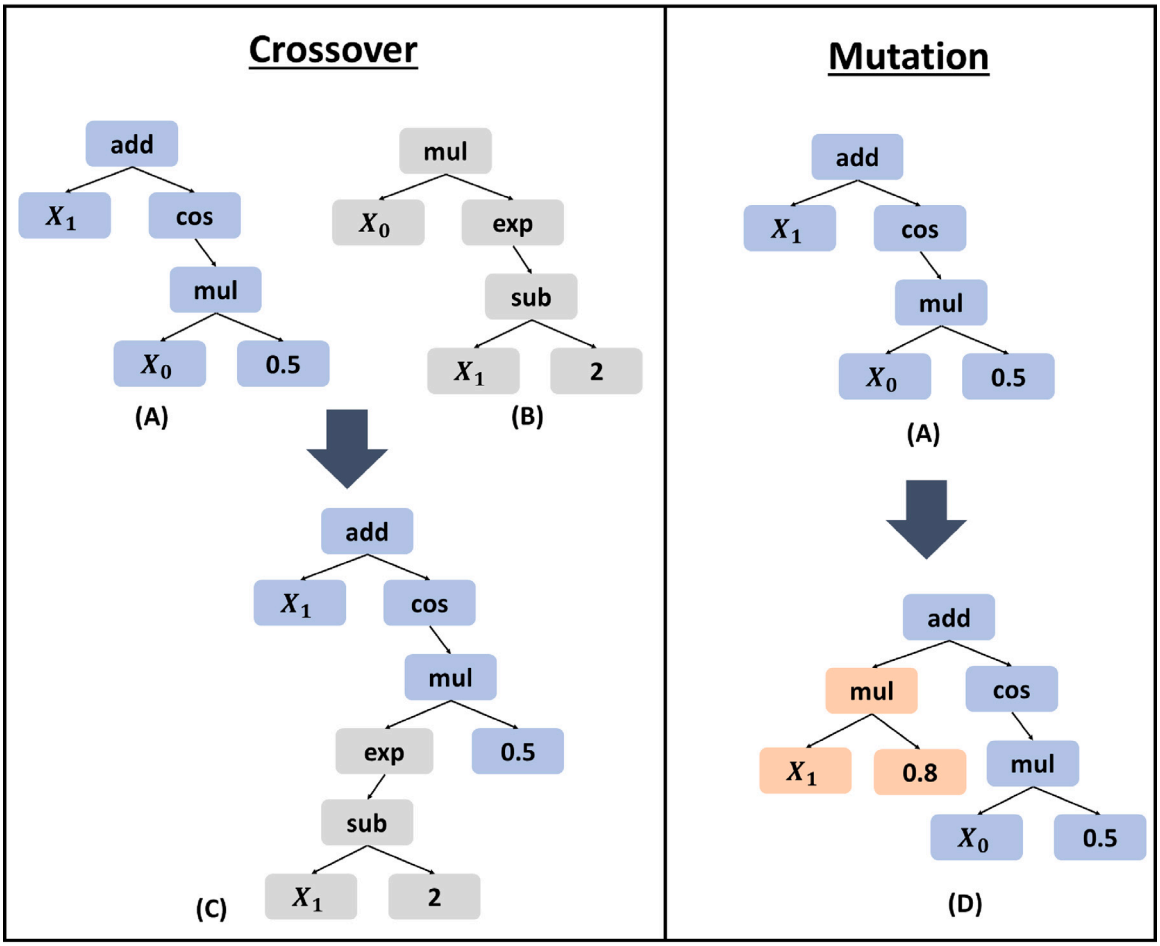

Fig. 11. Genetic operations in symbolic regression.

Another point is the difference in the number of parameters of ANNs, hybrid models and models developed by symbolic regression. The ANNs used in hybrid models usually present less parameters than single ANNs (Lima et al., 2023b), but there is still a huge amount of parameters compared to a phenomenological model. On the other hand, the equations obtained by symbolic regression presents a number of parameters similar to a phenomenological model. This can be observed in Nyande et al. (2024) study, in which the models obtained present similar structure to the population balance. Therefore, each ML approach presents advantages and disadvantages, and the choice of which one to use depends on the knowledge of the process and the application of the model. Symbolic regression is able to obtain simple equations that can efficiently describe the process (Wang et al., 2019). This characteristic is relevant for the development of an NMPC, as the optimization problem can be solved faster using this kind of model. Therefore, the use of models developed by symbolic regression as the internal model of and NMPC is a relevant application to be considered in future works.

The utilization of symbolic regression for modeling crystallization processes is a very recent development that offers many opportunities for application. The initial use by Nyande et al. (2024) showed that this approach has a potential to find equations that can effectively describe crystallization processes. Also, Quilló et al. (2021) demonstrated that the conventional approach to modeling crystallization processes, which does not account for the activity coefficient, can pose challenges in accurately representing these systems. Therefore, symbolic regression can be utilized to derive expressions, based on experimental data, that describe the CSD in a crystallization process, without relying on the simplifications typically assumed.

Regarding the various types of models presented and the detailed discussions on each, as developed throughout Section 2, Table 2 offers a comparative summary of the advantages and disadvantages of the models based on their type, along with potential issues that may arise in their selection for practical application. This comparison can also be extended to processes beyond crystallization, making it relevant for a wide range of PSE applications.

3. Machine learning for control of crystallization processes

General ML approaches are divided in three classes: supervised learning, unsupervised learning and reinforcement learning (Bishop, 2013). Supervised learning is characterized by considering information from the inputs and the outputs to develop the ML model. The neural network applications for crystallization processes discussed in Section 3.1 consider this kind of approach (Faria et al., 2022). In unsupervised learning, only information from the inputs are considered in the training. Clustering is an example that uses unsupervised learning (LeCun et al., 2015). Reinforcement learning (RL) is another ML approach that was recently used for controlling crystallization processes. Different from the other ML strategies, RL does not use any information of the inputs and outputs for its training. It discovers the most effective method to handle a task by repeatedly engaging with its environment (Sutton and Barto, 2018). Applications of RL to process control are discussed in Section 3.2.

Table 2
Comparison of model types: Advantages, Disadvantages, and Potential Problems.

Model type	Advantages	Disadvantages	Problems
Phenomenological models	– Interpretability and consistence – Generalization – Understanding of the system dynamics	– Requires detailed knowledge of the system – Computationally intensive – Less flexible	– Physics known
Empirical models	– Quick to develop – Can capture relationships in data without the full understanding of the physics underlined – Adaptable – Computationally efficient	– Lacks physical interpretability – Requires large datasets – Should not be used for extrapolation	– Availability of data – Physics unknown
Hybrid models	– Combine the strengths of phenomenological and empirical approaches – Improve accuracy and robustness	– May be difficult to implement – Involves higher computational costs than empirical models	– Availability of data – Physics known
Symbolic models	– Same as the empirical models – Interpretable models	– Should not be used for extrapolation	– Availability of data

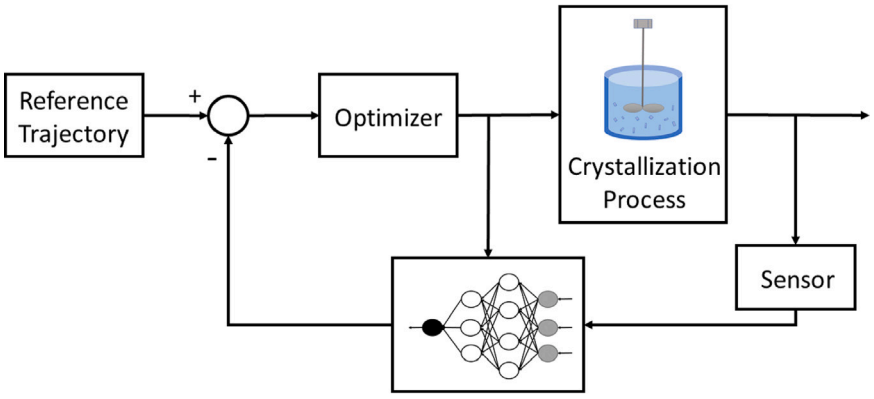

Fig. 12. Control loop of a crystallization process using an NMPC with ANN as the internal model.

3.1. Machine learning models applied for crystallization process control

NMPC is a control approach that makes use of an internal model to make predictions of the controlled variables and calculate the difference of these values to targets. One control approach that is commonly used for crystallization process is the application of a ML model as the internal model of an NMPC (Moraes et al., 2023). ANNs are ML model usually considered for the application of this methodology, as presented in Fig. 12.

Rohani et al. (1999) were the first to use an ANN as the internal model of an NMPC in a simulation study for controlling a crystallization process. They used this approach for controlling the continuous crystallization of potassium chloride. They demonstrated that the NMPC using ANN presented a better performance than a linear MPC using an autoregressive and an exogenous input (ARX) model. After these first application, more studies were developed using this approach. Fig. 13 presents the number of publications using ANNs as the internal model of MPC from 1999 to 2024 (Elsevier, 2024). As presented in Fig. 13, there was an increase in the number of publications using this approach in the last three years. The works published in the last 10 years using this methodology combining ANN to NMPC are presented in Table 3.

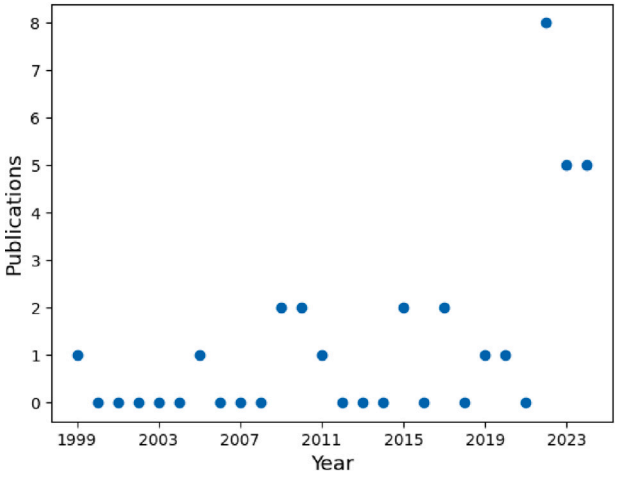

Fig. 13. Number of publications using neural networks as internal model of MPC for crystallization processes from 1999 to 2024 (Elsevier, 2024). Keywords: crystallization and (nmpc or mpc or "model predictive control" or "nonlinear model predictive control") and ("neural network" or ann), limited to engineering and chemical engineering fields.

Another approach that recently got more attention for crystallization control is neural network inverse model controller (NNIMC). In this methodology, an ANN is trained to predict the optimal control action to achieve the setpoint (Psichogios and Ungar, 1991). Therefore, instead of using the ANN to predict some characteristic of the crystallization such as the CSD, the ANN is used as the controller of the system (Daosud et al., 2005). A scheme of this approach is presented in Fig. 14. Kittisupakorn et al. (2017) first applied this methodology in a simulation study for controlling the terephthalic acid batch crystallization. They trained a feedforward network to predict the optimal temperature using current and past measurements of concentration and temperature as inputs. Recently, Sitapure and Kwon (2024) trained an LSTM network to be the controller of the dextrose batch crystallization in simulations. They used past measurements of the states as inputs and showed that the NNIMC presented a better performance than an NMPC using the LSTM network as its internal model for achieving the targets. Lima et al. (2024a) and Lima et al. (2024c) developed an NNIMC for controlling the paracetamol batch crystallization in ethanol for a simulation application. They concluded that the NNIMC could

Table 3
Publications using ANNs as the internal model of NMPCs for controlling crystallization processes in the last 10 years (Elsevier, 2024).

Study	System	Kind of neural network	Description
Meyer et al. (2024)	Batch crystallization of adipic acid and potassium dihydrogen phosphate (KDP)	MLP, GRU and LSTM	NMPC for controlling the crystal length and chord distribution in experiments
Sitapure and Kwon (2024)	Dextrose batch crystallization	LSTM	NMPC for controlling the concentration and the crystal mass in simulations
Moraes et al. (2023)	Potassium sulfate batch crystallization	ESN	Simulation application of an NMPC for controlling this system accounting for nucleation and crystal growth
Lima et al. (2023a)	Potassium sulfate batch crystallization	MLP	NMPC used in simulations for controlling this process considering nucleation, crystal growth and dissolution
Wu et al. (2023a) and Wu and Wu (2023)	Aspirin batch crystallization	PIRNN	NMPC for controlling the the crystal length and the coefficient of variation in simulations
Lima et al. (2022b)	Potassium sulfate batch crystallization	MLP and ESN	Simulation application of an NMPC for controlling the solution concentration
Zheng et al. (2022b), Zheng et al. (2022a) and Zheng and Wu (2022a)	Fesoterodine fumarate batch crystallization	Autoencoder-RNN	NMPC to optimize the product yield, crystal size, the quantity of fines in the product, and energy consumption in simulations
Zheng and Wu (2022b)	Fesoterodine fumarate batch crystallization	RNN	Simulation of NMPC based on RNN for controlling this process
Wang et al. (2022) and Wang and Zhu (2022)	–	RBF	NMPC for controlling a batch crystallization process in a lab-scale setup
Lima et al. (2022a)	Potassium sulfate batch crystallization	MLP and ESN	NMPC for controlling the first four moments of the CSD
Nielsen et al. (2020)	Lactose crystallization	Hybrid model with MLP	Simulation study using an NMPC based on the hybrid model for controlling the system
Szilagyi and Nagy (2019)	KDP batch crystallization	–	Simulation study applying ANN as a soft sensor and an NMPC using the measurements
Daosud et al. (2017)	Citric acid evaporative crystallization	MLP	Simulation application of an ANN as the internal model of an NMPC for controlling crystallization
Kittisupakorn et al. (2017)	Terephthalic acid batch crystallization	MLP	Simulation application of an ANN as the internal model of an NMPC for controlling crystallization
Li and Duan (2015) and Duan and Li (2015)	Sugar crystallization	–	Simulation applications of an ANN as the internal model of an NMPC for controlling crystallization

obtain the control action much faster than an NMPC in scenarios close to a real process accounting for noise. Oner et al. (2020) developed an NNIMC using RBF networks to control the chord length distribution in batch experiments of pharmaceutical crystallization process. They used Focused Beam Reflectance Measurement (FBRM) and the temperature as inputs of the network.

Another framework considered for controlling crystallization processes is the use of ML models combined with dynamic programming to obtain the control policy (Griffin et al., 2016; Grover et al., 2020). In this method, the ML model was created using Markovian dynamics within a simplified version of the system state, which includes two variables: crystal mass and chord count. Markov state models are a kind of statistical model used to describe the dynamics of systems that evolve over time (Perkett and Hagan, 2014). In this methodology, the system's state space is divided into discrete states, and the model captures the probabilities of transitioning from one state to another (Tang et al., 2017). Then, the data-driven model was used with dynamic programming to obtain the optimal temperature profiles to achieve the targets of crystal size and yield. This approach was used to control paracetamol (Grover et al., 2020) and $Na_3SO_4NO_3 \cdot H_2O$ (Griffin et al., 2016) crystallization in a lab-scale crystallizer.

One hybrid strategy used for controlling crystallization processes is the neuro-fuzzy control, which combines fuzzy logic and neural networks. By combining fuzzy logic and neural networks, the system takes the advantages of both approaches. Therefore, the fuzzy logic part handles imprecise and uncertain information, while the neural network part adapts and learns from the data to optimize performance (Sheikhzadeh et al., 2008; Jong et al., 2024). Sheikhzadeh et al. (2008) used this approach for controlling the paracetamol crystallization in water and isopropanol. They applied this method for controlling the supersaturation and the chord length counts by manipulating the temperature and the antisolvent addition. Recently, Jong et al. (2024) employed this strategy for the direct chord length control manipulating the temperature for the paracetamol with a p-acetoxyacetanilide system. Both Sheikhzadeh et al. (2008) and Jong et al. (2024) were able to implement this control technique in crystallization experiments.

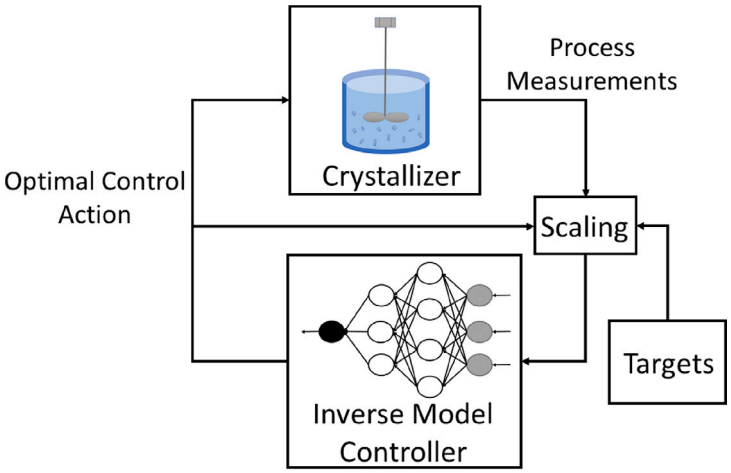

Fig. 14. Control loop of a crystallization process using an NNIMC as the controller.

The use of control methods based on ML models has recently gained more attention. As previously mentioned, ML models are able to describe crystallization processes using only data and make predictions faster than a population balance model. This characteristic is relevant for the development of model based control approaches, as the control action needs to be calculated within the sampling time in a real process. Lima et al. (2024c) concluded that an NNIMC was able to calculate the optimal control action around three times faster than an NMPC developed with a population balance model for paracetamol batch crystallization simulations accounting for noisy. As a consequence, this advantage of ML based control made more suitable the implementation of the control loop in experiments. The recent studies proposed by Grover et al. (2020), Wang et al. (2022) and Wang and Zhu (2022) and Meyer et al. (2024) are examples of control applications in the experimental setup enhanced by ML.

As presented in Fig. 12 by the sensor block, the measurements are a relevant part for the success of the control loop. The crystallization applications in the literature usually use attenuated total reflectance (ATR)-UV/vis, attenuated total reflection (ATR)-Fourier transform infrared (FTIR), Raman spectroscopy, focused beam reflectance measurement (FBRM), particle vision, and measurement (PVM) to make the process measurements (Nagy et al., 2008a; Griffin et al., 2017; Xiouras et al., 2022; Kim et al., 2023; Sun et al., 2024; Barhate et al., 2024). These sensors are able to take quick real-time measurements of multivariate spectra, images and chord length distributions. However, crystallization processes are usually modeled by population balance using the methods of moments (Nagy et al., 2008b,a; McDonald et al., 2019; Moraes et al., 2023; Kim et al., 2023). Therefore, in NMPC applications using the population balance model, a tool is necessary to convert ATR-FTIR and FBRM measurements into moments and concentration.

ML models are one alternative used to convert the FBRM and ATR-FTIR into the variables used by population balance models. Table 4 presents some works using ANN to convert the measurements of Raman, (ATR)-UV/vis, ATR-FTIR, FBRM and PVM into variables used in crystallization models. This is another way that ML models are applied to enable the real-time implementation of advanced control approaches in real crystallization processes. Regarding control applications, Szilagyi and Nagy (2019) developed PVM and FBRM sensors based on ANNs. These sensors converted the two-dimensional crystal size distribution into chord length distribution and aspect ratio distribution across arbitrary two-dimensional grids. The ANN-based soft sensor was employed to simulate the most probable average value of the bivariate crystal size distribution (2D CSD) and assist in guiding experiments to control the crystal size and shape. Wang et al. (2022) and Wang and Zhu (2022) trained CNNs that used the images of the PVM as inputs to calculate the crystal sized and area. The information obtained by the CNNs was used by an NMPC to control a batch crystallization process. Moreover, Griffin et al. (2016) developed a calibration curve based on ATR-FTIR measurements to calculate the concentration of the solution and, consequently, the crystal mass in a batch crystallization process. The crystal mass and FBRM measurements of the chord count were used as inputs of a ML model. The proposed model was used to control the yield and the crystal size in batch experiments of $Na_3SO_4NO_3 \cdot H_2O$ crystallization.

Another point that is relevant for real-time implementation of control strategies is the availability of an efficient solubility model. As previously discussed, for crystallization of a solute in a single solvent, modeling solubility is relatively straightforward, as it depends primarily on temperature (Worlitschek and Mazzotti, 2004; Kim et al., 2023). However, when an antisolvent is added, the system becomes a ternary mixture, where solubility depends on both temperature and the composition of the solvent and antisolvent (O'Ciardhá et al., 2012). To model this kind of system, thermodynamic models like non-random two-liquid (NRTL) and UNIQUAC may be a solution (Assis et al., 2021; Romdhani et al., 2020). However, this kind of model may not be suitable for real-time implementations because of their complex structure, demanding time to calculate the solubility. To avoid this issue, ML models were used to calculate the solubility and perform real-time control of antisolvent crystallization. This kind of application was proposed by Nagy et al. (2008a) and used to control the lovastatin crystallization in acetone-water mixture in an experimental setup.

ML models enabled many advances in the implementation of advanced control approaches in real crystallization processes. Even with these developments, there are opportunities of new applications. Different approaches were proposed but they were not compared. Defining which methodology is the best for controlling a crystallization process is a relevant topic. Some ML model approaches previously presented still need to be applied for the development of control approaches for crystallization processes. Moreover, most control applications using ML models for crystallization processes are simulation studies. There are only few works that used this methodology for experimental applications (Griffin et al., 2016; Grover et al., 2020; Meyer et al., 2024; Wang et al., 2022; Wang and Zhu, 2022). The use of these methodologies in real crystallization processes is a fundamental topic to be considered in future studies.

3.2. Control approaches based on reinforcement learning

Different from the other ML strategies, reinforcement learning does not use any information of the inputs and outputs for its training.

Table 4
An overview of the studies ANNs to convert the PAT measurements into the variables used in population balance models.

Study	System	Description
Saleemi et al. (2012)	Ortho and para-aminobenzoic acid crystallization	Convert ATR-UV/vis spectroscopy in concentration
Szilágyi and Nagy (2018)	Pharmaceutical batch crystallization	Converted FBRM and PVM measurements to CSD
Barmpalexis et al. (2018)	Carbamazepine in nicotinamide and ibuprofen in nicotinamide	Used Raman and ATR-FTIR spectroscopy to the determination of cocrystal content
Lin et al. (2020)	Paracetamol in ethanol and L-glutamic acid in water	Converted Raman spectroscopy to solution and solids concentration
Crestani et al. (2021)	Sucrose crystallization	Converted chord length distribution measurements from FBRM to particle size distribution
Gavran et al. (2023)	Ceritinib crystallization	Converted Raman spectroscopy to solute concentration

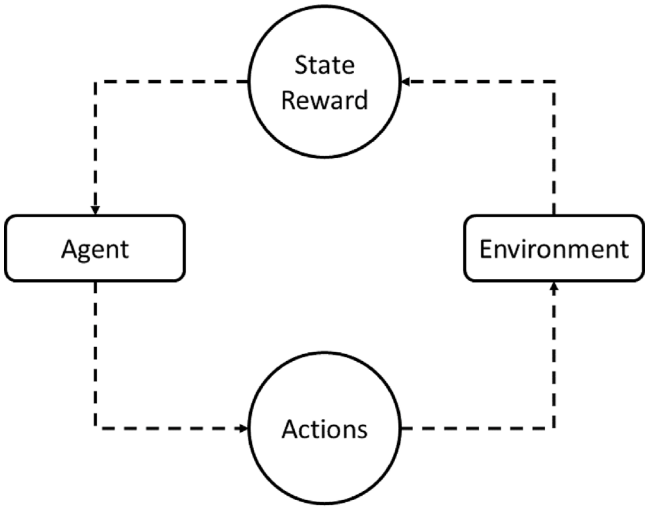

Fig. 15. Reinforcement learning methodology.

It discovers the most effective method to handle a task by repeatedly engaging with its environment (Sutton and Barto, 2018). Fig. 15 provides a brief overview of the reinforcement learning concept. A reinforcement learning problem is composed of an agent interacting with the environment through actions, leading to a new state, and being guided by a reward (Faria et al., 2023). Therefore, the reinforcement learning consists of an optimization problem to find the actions that optimize the reward function (Faria et al., 2024).

Reinforcement learning is used for process control in a dynamic programming problem (Shin et al., 2019). Therefore, the actions in Fig. 15 are the control actions, the environment is the process, the agent is the controller, the states are the state variables and the reward function is the objective function of the dynamic programming. The goal of this optimization problem is to find the optimum policy of the control actions that minimizes the difference between the controlled variables and the targets (Nian et al., 2020).

The use of reinforcement learning for controlling crystallization processes represents a recent development in the literature. Reinforcement learning was first applied for controlling crystallization processes by Zhang et al. (2020) for obtaining the control policies to determine which field shapes and orientations should be actuated to fast remove grain boundaries and restore circular crystal morphologies from anisotropic states. After this first application, the other studies that used reinforcement learning for controlling crystallization processes are presented in Table 5.

Therefore, reinforcement learning can be tested for controlling other crystallization systems in future works, focusing on experimental applications. There are also opportunities for developing works focusing on enhancing the current control approaches based on reinforcement learning for crystallization processes.

4. Conclusions, challenges and future directions

The ML techniques have emerged and significantly enhanced how engineers and scientists handle and interpret data. By integrating ML, researchers gain improved computational efficiency, ease of application, and versatility, which are crucial for advancing both research and practical applications. In crystallization processes, the ML technologies have further enhanced predictive capabilities of crystalline properties and crystal quality, real-time monitoring, and optimal/adaptative control strategies.

The complex and often poorly understood processes of crystal growth, nucleation, and crystal agglomeration, aggregation and breakage mechanisms make it difficult to create accurate models using traditional first-principles methods. ML can offer a solution by utilizing the obtained models and historical data to map multiple descriptors to new ones, uncovering patterns and information from extensive datasets. In crystallization, this approach has improved research efficiency and applicability in areas such as crystal characterization, structure–property relationships, solid and liquid phase predictions, and process control.

For complex systems where classical models face challenges, ML provides valuable insights by handling high-dimensional data and identifying nonlinear relationships. However, ML should not be seen as an isolated and decisive answer to all crystallization challenges. To achieve optimal performance, careful selection of algorithms, hyperparameter tuning, and data preprocessing are essential. Additionally, certain areas of crystallization research, such as predicting crystal structures, understanding nucleation, breakage and aggregation mechanisms continue to present difficulties that ML alone cannot fully address.

Hybrid models that merge first-principles and ML can improve predictive accuracy and offer a more comprehensive understanding of crystallization. ML can refine and calibrate first-principles models, addressing parameter estimation, and incorporating experimental data that theoretical models might overlook. Combining conventional first-principles models with data-driven ML methods can bridge the gap between scientific understanding and practical application, leading to more robust and reliable predictions for quality tasks regarding the crystal product size, shape, and form. Additionally, establishing standardized evaluation systems for fair model comparisons and their involved criteria will be essential. Advancements in these areas will drive progress in crystallization research and intelligent manufacturing, underscoring the need for interdisciplinary integration.

In addition to predictive modeling, ML technologies facilitate real-time monitoring and optimal control of crystallization processes. The application of data driven controllers in crystallization processes is highlighted. Therefore, machine learning algorithms to process data

Table 5
Studies developed using reinforcement learning for controlling crystallization processes.

Year	Publication
2023	Meng et al. (2023) used reinforcement learning in simulations to control they crystal size in KDP crystallization in water and crystallization of aspirin in ethanol and water. In the first system, the temperature was the manipulated variable, while antisolvent addition and temperature were manipulated in the other system.
2022	Anandan et al. (2022) develop an inverse reinforcement learning approach for controlling paracetamol batch crystallization. The ML was trained with using crystallization processes controlled by PID and MPC and applied in simulations of paracetamol crystallization.
	Manee et al. (2022) used CNN as a softer sensor and reinforcement learning for controlling sodium chloride crystallization in water using ethanol as antisolvent. They manipulated the temperature and the antisolvent addition to control the crystal size in an experimental setup.
2021	Benyahia et al. (2021a) proposed a trajectory tracking control strategy based on reinforcement learning. They applied this methodology in simulations for controlling the crystal mean size, crystal size distribution, purity and crystal shape in simulations of batch crystallization of paracetamol in water.
	Benyahia et al. (2021b) developed a trajectory tracking control strategy based on reinforcement learning and applied this approach in simulations of batch and continuous crystallization of paracetamol in water. They controlled the crystal size by manipulating the temperature.
	Manee et al. (2021) used reinforcement learning for controlling the crystallization of NaCl in a water-ethanol system. They manipulated the antisolvent addition and the temperature to control the mean crystal size and efficiently applied this control loop in an experimental setup.

from sensors and imaging systems to continuously assess crystal target specifications and quality during production stand out.

Despite these advancements, several challenges persist, including the high costs and maintenance of automated systems and data management using the current PATs measurement techniques in crystallization processes. Addressing these challenges involves developing automated high-throughput screening systems, improving in situ characterization technologies, while managing data and model limitations. Future efforts should focus on optimizing data quality and features, preventing model overfitting, and leveraging comprehensive datasets for more effective operations in crystallization.

There are also challenges regarding the implementation of ML based methodologies in industrial crystallization processes. According to Arden et al. (2021), the pharmaceutical field is on a transition from industry 2.0 to 3.0, adopting continuous manufacturing and employing advanced PAT. Future developments should also focus on implement ML based modeling and control methodologies in industrial crystallization processes, promoting a more automated system and products with higher quality.

CRediT authorship contribution statement

Fernando Arrais R.D. Lima: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Marcellus G.F. de Moraes:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Amaro G. Barreto Jr:** Writing – review & editing, Conceptualization. **Argimiro R. Secchi:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Martha A. Grover:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Maurício B. de Souza Jr:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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.

Acknowledgments

The authors acknowledge funding from the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES, Finance Code 001), the National Council for Scientific and Technological Development (CNPq, Grants 303587/2020-2, 311153/2021-6, and 313337/2021-7), and the Research Support Foundation of the State of Rio de Janeiro (FAPERJ, Grants E 26/111.671/2013 and E-26/201.148/2022).

References

Abdi-Khanghah, M., Bemani, A., Naserzadeh, Z., Zhang, Z., 2018. Prediction of solubility of N-alkanes in supercritical CO2 using RBF-ANN and MLP-ANN. J. CO2 Util. 25, 108–119. http://dx.doi.org/10.1016/j.jcou.2018.03.008.

An, N., Kwon, H., Cho, H., Kim, J., 2022. Data-driven modeling for magma density in the continuous crystallization process. In: Yamashita, Y., Kano, M. (Eds.), 14th International Symposium on Process Systems Engineering. In: Computer Aided Chemical Engineering, vol. 49, Elsevier, pp. 1813–1818. http://dx.doi.org/10.1016/B978-0-323-85159-6.50302-X.

Anandan, P.D., Rielly, C.D., Benyahia, B., 2022. Optimal control policies of a crystallization process using inverse reinforcement learning. In: Montastruc, L., Negny, S. (Eds.), 32nd European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, 51, Elsevier, pp. 1093–1098. http://dx.doi.org/10.1016/B978-0-323-95879-0.50183-1, URL: https://www.sciencedirect.com/science/article/pii/B9780323958790501831.

Antonelo, E.A., Camponogara, E., Foss, B., 2017. Echo state networks for data-driven downhole pressure estimation in gas-lift oil wells. Neural Netw. 85, 106–117. http://dx.doi.org/10.1016/j.neunet.2016.09.009.

Arden, N.S., Fisher, A.C., Tyner, K., Yu, L.X., Lee, S.L., Kopcha, M., 2021. Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future. Int. J. Pharm. 602, 120554. http://dx.doi.org/10.1016/j.ijpharm.2021.120554.

Assis, G.P., Garcia, R.H.L., Derenzo, S., Bernardo, A., 2021. Solid-liquid equilibrium of paracetamol in water-ethanol and water-propylene glycol mixtures. J. Mol. Liq. 323, 114617. http://dx.doi.org/10.1016/j.molliq.2020.114617.

Barhate, Y., Kilari, H., Wu, W.-L., Nagy, Z.K., 2024. 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. 287, 119688. http://dx.doi.org/10.1016/j.ces.2023.119688.

Barmpalexis, P., Karagianni, A., Nikolakakis, I., Kachrimanis, K., 2018. Artificial neural networks (ANNs) and partial least squares (PLS) regression in the quantitative analysis of cocrystal formulations by Raman and ATR-FTIR spectroscopy. J. Pharm. Biomed. Anal. 158, 214–224. http://dx.doi.org/10.1016/j.jpba.2018.06.004.

Baughman, D.R., Liu, Y.A., 2014. Neural Networks in Bioprocessing and Chemical Engineering. Academic Press.

Benyahia, B., Anandan, P., Rielly, C., 2021a. Robust model-based reinforcement learning control of a batch crystallization process. In: 2021 9th International Conference on Systems and Control. ICSC, pp. 89–94. http://dx.doi.org/10.1109/ICSC50472.2021.9666494.

Benyahia, B., Anandan, P.D., Rielly, C., 2021b. Control of batch and continuous crystallization processes using reinforcement learning. In: Türkay, M., Gani, R. (Eds.), 31st European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 50, Elsevier, pp. 1371–1376. http://dx.doi.org/10.1016/B978-0-323-88506-5.50211-4.

Bishop, C.M., 2013. Pattern Recognition and Machine Learning: All" just the Facts 101" Material. Cram101.

Bo, Y.-C., Zhang, X., 2018. Online adaptive dynamic programming based on echo state networks for dissolved oxygen control. Appl. Soft Comput. 62, 830–839. http://dx.doi.org/10.1016/j.asoc.2017.09.015.

Braatz, R.D., 2002. Advanced control of crystallization processes. Annu. Rev. Control 26 (1), 87–99. http://dx.doi.org/10.1016/s1367-5788(02)80016-5.

Brunton, S.L., Proctor, J.L., Kutz, J.N., 2016. Discovering governing equations from data by sparse identification of nonlinear dynamical systems. Proc. Natl. Acad. Sci. 113 (15), 3932–3937. http://dx.doi.org/10.1073/pnas.1517384113.

Cai, S., Mao, Z., Wang, Z., Yin, M., Karniadakis, G.E., 2021. Physics-informed neural networks (PINNs) for fluid mechanics: A review. Acta Mech. Sin. 37 (12), 1727–1738. http://dx.doi.org/10.1007/s10409-021-01148-1.

Chen, K., Rögnvaldsson, T., Nowaczyk, S., Pashami, S., Klang, J., Sternelöv, G., 2023. Material handling machine activity recognition by context ensemble with gated recurrent units. Eng. Appl. Artif. Intell. 126, 106992. http://dx.doi.org/10.1016/j.engappai.2023.106992.

Cohen, B., Beykal, B., Bollas, G.M., 2023. Physics-informed genetic programming for discovery of partial differential equations from scarce and noisy data. http://dx.doi.org/10.2139/ssrn.4604759, Available at SSRN 4604759.

Costa, E.A., de Menezes Rebello, C., Santana, V.V., Reges, G., de Oliveira Silva, T., de Abreu, O.S.L., Ribeiro, M.P., Foresti, B.P., Fontana, M., dos Reis Nogueira, I.B., et al., 2024. An uncertainty approach for electric submersible pump modeling through deep neural network. Heliyon 10 (2), http://dx.doi.org/10.1016/j.heliyon.2024.e24047.

Costa, E.A., Rebello, C.d., Fontana, M., Schnitman, L., Nogueira, I.B.d.R., 2023. A robust learning methodology for uncertainty-aware scientific machine learning models. Math. 11 (1), http://dx.doi.org/10.3390/math11010074.

Costa, E.A., Rebello, C.M., Santana, V.V., Rodrigues, A.E., Ribeiro, A.M., Schnitman, L., Nogueira, I.B.R., 2022. Mapping uncertainties of soft-sensors based on deep feedforward neural networks through a novel Monte Carlo uncertainties training process. Processes 10 (2), http://dx.doi.org/10.3390/pr10020409.

Cranmer, M., 2023. Interpretable machine learning for science with PySR and SymbolicRegression. jl. http://dx.doi.org/10.48550/arXiv.2305.01582, arXiv preprint arXiv:2305.01582.

Crestani, C., Bernardo, A., Costa, C., Giulietti, M., 2021. An artificial neural network model applied to convert sucrose chord length distributions into particle size distributions. Powder Technol. 384, 186–194. http://dx.doi.org/10.1016/j.powtec.2021.01.075.

Daosud, W., Thampasato, J., Kittisupakorn, P., 2017. Neural network based modeling and control for a batch heating/cooling evaporative crystallization process. Eng. J. 21 (1), 127–144. http://dx.doi.org/10.4186/ej.2017.21.1.127.

Daosud, W., Thitiyasook, P., Arpornwichanop, A., Kittisupakorn, P., Hussain, M.A., 2005. Neural network inverse model-based controller for the control of a steel pickling process. Comput. Chem. Eng. 29 (10), 2110–2119. http://dx.doi.org/10.1016/j.compchemeng.2005.06.007.

Deihim, A., Alonso, E., Apostolopoulou, D., 2023. Sttre: A spatio-temporal transformer with relative embeddings for multivariate time series forecasting. Neural Netw. 168, 549–559. http://dx.doi.org/10.1016/j.neunet.2023.09.039.

Devogelaer, J.-J., Charpentier, M.D., Tijink, A., Dupray, V., Coquerel, G., Johnston, K., Meekes, H., Tinnemans, P., Vlieg, E., ter Horst, J.H., de Gelder, R., 2021. Cocrystals of praziquantel: Discovery by network-based link prediction. Cryst. Growth Des. 21 (6), 3428–3437. http://dx.doi.org/10.1021/acs.cgd.1c00211, URL: https://pubs.acs.org/doi/10.1021/acs.cgd.1c00211.

Dias, A.C.S.R., Soares, F.R., Jäschke, J., Souza, Jr., M.B., Pinto, J.C., 2019. Extracting valuable information from big data for machine learning control: An application for a gas lift process. Processes 7 (5), http://dx.doi.org/10.3390/pr7050252.

Duan, H., Li, Q., 2015. Sugar precipitation control of Chinese medicine solution based on nonlinear model predictive. In: 2015 7th International Conference on Intelligent Human-Machine Systems and Cybernetics. Vol. 1, pp. 66–69. http://dx.doi.org/10.1109/IHMSC.2015.267.

Eisenschmidt, H., Bajcinca, N., Sundmacher, K., 2016. Optimal control of crystal shapes in batch crystallization experiments by growth-dissolution cycles. Cryst. Growth Des. 16 (6), 3297–3306. http://dx.doi.org/10.1021/acs.cgd.6b00288, URL: https://pubs.acs.org/doi/10.1021/acs.cgd.6b00288.

Elsevier, B.V., 2024. Scopus. URL: https://www.elsevier.com/products/scopus. (Accessed 27 November 2024).

Elsheikh, A.H., Katekar, V.P., Muskens, O.L., Deshmukh, S.S., Elaziz, M.A., Dabour, S.M., 2021. Utilization of LSTM neural network for water production forecasting of a stepped solar still with a corrugated absorber plate. Process Saf. Environ. Prot. 148, 273–282. http://dx.doi.org/10.1016/j.psep.2020.09.068.

Faria, R.d.R., Capron, B.D.O., Secchi, A.R., de Souza, Jr., M.B., 2022. Where reinforcement learning meets process control: Review and guidelines. Processes 10 (11), 2311. http://dx.doi.org/10.3390/pr10112311.

Faria, R.R., Capron, B., Secchi, A.R., de Souza, Jr., M.B., 2024. A data-driven tracking control framework using physics-informed neural networks and deep reinforcement learning for dynamical systems. Eng. Appl. Artif. Intell. 127, 107256. http://dx.doi.org/10.1016/j.engappai.2023.107256.

Faria, R.d.R., Capron, B.D.O., de Souza, Jr., M.B., Secchi, A.R., 2023. One-layer real-time optimization using reinforcement learning: A review with guidelines. Processes 11 (1), 123. http://dx.doi.org/10.3390/pr11010123.

Fujiwara, M., Nagy, Z.K., Chew, J.W., Braatz, R.D., 2005. First-principles and direct design approaches for the control of pharmaceutical crystallization. J. Process Control 15 (5), 493–504. http://dx.doi.org/10.1016/j.jprocont.2004.08.003.

Fukami, K., Murata, T., Zhang, K., Fukagata, K., 2021. Sparse identification of nonlinear dynamics with low-dimensionalized flow representations. J. Fluid Mech. 926, A10. http://dx.doi.org/10.1017/jfm.2021.697.

Galvanauskas, V., Georgieva, P., de Azevedo, S., 2006. Dynamic optimisation of industrial sugar crystallization process based on a hybrid (mechanistic+ANN) model. In: The 2006 IEEE International Joint Conference on Neural Network Proceedings. pp. 2728–2735. http://dx.doi.org/10.1109/IJCNN.2006.247177.

Gan, C., Wang, L., Xiao, S., Zhu, Y., 2022. Feedback control of crystal size distribution for cooling batch crystallization using deep learning-based image analysis. Crystals 12 (5), http://dx.doi.org/10.3390/cryst12050570.

Gao, Z., Rohani, S., Gong, J., Wang, J., 2017. Recent developments in the crystallization process: Toward the pharmaceutical industry. Engineering 3 (3), 343–353. http://dx.doi.org/10.1016/J.ENG.2017.03.022.

Gavran, M., Ujević Andrijić, Ž., Bolf, N., Rimac, N., Sacher, J., Šahnić, D., 2023. Development of a calibration model for real-time solute concentration monitoring during crystallization of ceritinib using Raman spectroscopy and in-line process microscopy. Processes 11 (12), http://dx.doi.org/10.3390/pr11123439.

Georgieva, P., Meireles, M., Feyo de Azevedo, S., 2003. Knowledge-based hybrid modelling of a batch crystallisation when accounting for nucleation, growth and agglomeration phenomena. Chem. Eng. Sci. 58 (16), 3699–3713. http://dx.doi.org/10.1016/S0009-2509(03)00260-4.

Golhani, K., Balasundram, S.K., Vadamalai, G., Pradhan, B., 2018. A review of neural networks in plant disease detection using hyperspectral data. Inf. Process. Agric. 5 (3), 354–371. http://dx.doi.org/10.1016/j.inpa.2018.05.002.

Griffin, D.J., Grover, M.A., Kawajiri, Y., Rousseau, R.W., 2016. Data-driven modeling and dynamic programming applied to batch cooling crystallization. Ind. Eng. Chem. Res. 55 (5), 1361–1372. http://dx.doi.org/10.1021/acs.iecr.5b03635.

Griffin, D.J., Kawajiri, Y., Rousseau, R.W., Grover, M.A., 2017. Using MC plots for control of paracetamol crystallization. Chem. Eng. Sci. 164, 344–360. http://dx.doi.org/10.1016/j.ces.2017.01.065.

Grover, M.A., Griffin, D.J., Tang, X., Kim, Y., Rousseau, R.W., 2020. Optimal feedback control of batch self-assembly processes using dynamic programming. J. Process Control 88, 32–42. http://dx.doi.org/10.1016/j.jprocont.2020.01.013.

Guardani, R., Onimaru, R.S., Crespo, F.C.d., 2001. Neural network model for the on-line monitoring of a crystallization process. Br. J. Chem. Eng. 18 (3), 267–275. http://dx.doi.org/10.1590/S0104-66322001000300006.

Heisel, S., Holtkötter, J., Wohlgemuth, K., 2019. Measurement of agglomeration during crystallization: Is the differentiation of aggregates and agglomerates via ultrasonic irradiation possible? Chem. Eng. Sci. 210, 115214. http://dx.doi.org/10.1016/j.ces.2019.115214.

Heisel, S., Rolfes, M., Wohlgemuth, K., 2018. Discrimination between single crystals and agglomerates during the crystallization process. Chem. Eng. Technol. 41 (6), 1218–1225. http://dx.doi.org/10.1002/ceat.201700651.

Heng, T., Yang, D., Wang, R., Zhang, L., Lu, Y., Du, G., 2021. Progress in research on artificial intelligence applied to polymorphism and cocrystal prediction. ACS Omega 6 (24), 15543–15550. http://dx.doi.org/10.1021/acsomega.1c01330, URL: https://pubs.acs.org/doi/10.1021/acsomega.1c01330.

Hong, J., Yang, H., Ma, F., 2023. Multi-forward-step battery voltage prediction for real-world electric vehicles using gated recurrent units. J. Energy Storage 73, 109056. http://dx.doi.org/10.1016/j.est.2023.109056.

Hornik, K., Stinchcombe, M., White, H., 1989. Multilayer feedforward networks are universal approximators. Neural Netw. http://dx.doi.org/10.1016/0893-6080(89)90020-8.

Inapakurthi, R.K., Miriyala, S.S., Mitra, K., 2021. Deep learning based dynamic behavior modelling and prediction of particulate matter in air. Chem. Eng. J. 426, 131221. http://dx.doi.org/10.1016/j.cej.2021.131221.

Jong, C.Y., Mittal, A., Tristan, G., Noller, V., Chan, H.L., Goh, Y., Yeap, E.W.Q., Dubbaka, S.R., Nagesh, H.R., Wong, S.Y., 2024. Anfis-driven machine learning automated platform for cooling crystallization process development. Org. Process Res. Dev. 28 (4), 1129–1144. http://dx.doi.org/10.1021/acs.oprd.3c00505.

Kay, H., Kay, S., Mowbray, M., Lane, A., Mendoza, C., Martin, P., Zhang, D., 2023. Symbolic regression based interpretable data-driven soft-sensor for process quality control. In: Kokossis, A.C., Georgiadis, M.C., Pistikopoulos, E. (Eds.), 33rd European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 52, Elsevier, pp. 1525–1530. http://dx.doi.org/10.1016/B978-0-443-15274-0.50243-2.

Kim, Y., Kawajiri, Y., Rousseau, R.W., Grover, M.A., 2023. Modeling of nucleation, growth, and dissolution of paracetamol in ethanol solution for unseeded batch cooling crystallization with temperature-cycling strategy. Ind. Eng. Chem. Res. 62 (6), 2866–2881. http://dx.doi.org/10.1021/acs.iecr.2c03465.

Kittisupakorn, P., Somsong, P., Hussain, M.A., Daosud, W., 2017. Improving of crystal size distribution control based on neural network-based hybrid model for purified terephthalic acid batch crystallizer. Eng. J. 21 (7), 319–331. http://dx.doi.org/10.4186/ej.2017.21.7.319.

Kumar, R., Aggarwal, R., Sharma, J., 2013. Energy analysis of a building using artificial neural network: A review. Energy Build. 65, 352–358. http://dx.doi.org/10.1016/j.enbuild.2013.06.007.

Kurban, T., Beşdok, E., 2009. A comparison of RBF neural network training algorithms for inertial sensor based terrain classification. Sensors 9 (8), 6312–6329. http://dx.doi.org/10.3390/s90806312.

Lauret, P., Boyer, H., Gatina, J.-C., 2001. Hybrid modelling of the sucrose crystal growth rate. Int. J. Modelling Simul. 21 (1), 23–29. http://dx.doi.org/10.1080/02286203.2001.11442183.

LeCun, Y., Bengio, Y., Hinton, G., 2015. Deep learning. Nature 521, 436–444. http://dx.doi.org/10.1038/nature14539.

Lee, E.H., 2014. A practical guide to pharmaceutical polymorph screening & selection. Asian J. Pharm. Sci. 9 (4), 163–175. http://dx.doi.org/10.1016/j.ajps.2014.05.002.

Li, Q., Duan, H., 2015. Model predictive control of a Chinese medicine sugar precipitation process. In: Proceeding of the 11th World Congress on Intelligent Control and Automation. pp. 4850–4853. http://dx.doi.org/10.1109/WCICA.2014.7053535.

Li, H., Kawajiri, Y., Grover, M.A., Rousseau, R.W., 2017. Modeling of nucleation and growth kinetics for unseeded batch cooling crystallization. Ind. Eng. Chem. Res. 56 (14), 4060–4073. http://dx.doi.org/10.1021/acs.iecr.6b04914, arXiv:https://doi.org/10.1021/acs.iecr.6b04914.

Li, J., Qin, S.J., 2023. Applying and dissecting LSTM neural networks and regularized learning for dynamic inferential modeling. Comput. Chem. Eng. 175, 108264. http://dx.doi.org/10.1016/j.compchemeng.2023.108264.

Liao, Y., Wang, W., Zhang, Z., Zhao, S., Niu, Y., Liu, X., 2022. A novel method based on adaptive autoencoder and improved long short-term memory and gated recurrent unit for nuclear radiation measurement and monitoring. Measurement 199, 111571. http://dx.doi.org/10.1016/j.measurement.2022.111571.

Lillicrap, T.P., Santoro, A., 2019. Backpropagation through time and the brain. Curr. Opin. Neurobiol. 55, 82–89. http://dx.doi.org/10.1016/j.conb.2019.01.011, Machine Learning, Big Data, and Neuroscience.

Lima, F.A.R.D., Barreto Correa, G., de Moraes, M.G.F., Segtovich, I.S.V., Barreto Junior, A.G., Pinto, J.C., 2024b. Statistical analyses of a population balance model of a batch crystallization process. Cryst. Growth Des. 24 (1), 308–324. http://dx.doi.org/10.1021/acs.cgd.3c01027.

Lima, F.A.R., de Miranda, G.F., Moraes, M.G., Capron, B.D., Souza, M.B., 2022a. A recurrent neural networks-based approach for modeling and control of a crystallization process. In: Montastruc, L., Negny, S. (Eds.), 32nd European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 51, Elsevier, pp. 1423–1428. http://dx.doi.org/10.1016/B978-0-323-95879-0.50238-1.

Lima, F.A.R.D., de Moraes, M.G.F., Grover, M.A., Barreto Junior, A.G., Secchi, A.R., de Souza, M.B.J., 2024c. Neural network inverse model controllers for paracetamol unseeded batch cooling crystallization. Ind. Eng. Chem. Res. 63 (45), 19613–19627. http://dx.doi.org/10.1021/acs.iecr.4c02060.

Lima, F.A.R., Moraes, M.G., Barreto, A.G., Secchi, A.R., Souza, Jr., M.B., 2023a. An NN-NMPC for controlling a crystallization process in the saturated and undersaturated zones. In: Kokossis, A.C., Georgiadis, M.C., Pistikopoulos, E. (Eds.), 33rd European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 52, Elsevier, pp. 1835–1840. http://dx.doi.org/10.1016/B978-0-443-15274-0.50291-2.

Lima, F.A.R., Moraes, M.G., Grover, M.A., Barreto, A.G., Secchi, A.R., Souza, M.B., 2024a. Controlling paracetamol unseeded batch crystallization with NMPC and inverse model. IFAC-PapersOnLine 58 (14), 31–36. http://dx.doi.org/10.1016/j.ifacol.2024.08.309, 12th IFAC Symposium on Advanced Control of Chemical Processes ADCHEM 2024.

Lima, F.A.R.D., Moraes, M.G.F., Secchi, A.R., Souza, Jr., M.B., 2022b. Development of a recurrent neural networks-based NMPC for controlling the concentration of a crystallization process. Digit. Chem. Eng. 5, 100052. http://dx.doi.org/10.1016/j.dche.2022.100052.

Lima, F.A.R., Rebello, C.M., Costa, E.A., Santana, V.V., de Moares, M.G., Barreto, A.G., Secchi, A.R., de Souza, M.B., Nogueira, I.B., 2023b. Improved modeling of crystallization processes by universal differential equations. Chem. Eng. Res. Des. http://dx.doi.org/10.1016/j.cherd.2023.11.032.

Lin, M., Wu, Y., Rohani, S., 2020. Simultaneous measurement of solution concentration and slurry density by Raman spectroscopy with artificial neural network. Cryst. Growth Des. 20 (3), 1752–1759. http://dx.doi.org/10.1021/acs.cgd.9b01482.

Lu, M., Rao, S., Yue, H., Han, J., Wang, J., 2024. Recent advances in the application of machine learning to crystal behavior and crystallization process control. Cryst. Growth Des. 24 (12), 5374–5396. http://dx.doi.org/10.1021/acs.cgd.3c01251.

Ma, S., Li, C., Gao, J., Yang, H., Tang, W., Gong, J., Zhou, F., Gao, Z., 2020. Artificial neural network prediction of metastable zone widths in reactive crystallization of lithium carbonate. Ind. Eng. Chem. Res. 59 (16), 7765–7776. http://dx.doi.org/10.1021/acs.iecr.9b06074.

Manee, V., Baratti, R., Romagnoli, J.A., 2021. Optimal strategies to control particle size and variance in antisolvent crystallization operations using deep rl. Chem. Eng. Trans. 86, 943–948. http://dx.doi.org/10.3303/CET2186158.

Manee, V., Baratti, R., Romagnoli, J.A., 2022. Learning to navigate a crystallization model with deep reinforcement learning. Chem. Eng. Res. Des. 178, 111–123. http://dx.doi.org/10.1016/j.cherd.2021.12.005.

Manee, V., Zhu, W., Romagnoli, J.A., 2019. A deep learning image-based sensor for real-time crystal size distribution characterization. Ind. Eng. Chem. Res. 58 (51), 23175–23186. http://dx.doi.org/10.1021/acs.iecr.9b02450.

Mann, V., Venkatasubramanian, V., 2021. Predicting chemical reaction outcomes: A grammar ontology-based transformer framework. AIChE J. 67 (3), e17190. http://dx.doi.org/10.1002/aic.17190.

Matino, I., Dettori, S., Colla, V., Weber, V., Salame, S., 2019. Forecasting blast furnace gas production and demand through echo state neural network-based models: Pave the way to off-gas optimized management. Appl. Energy 253, 113578. http://dx.doi.org/10.1016/j.apenergy.2019.113578.

McBride, K., Sundmacher, K., 2019. Overview of surrogate modeling in chemical process engineering. Chem. Ing. Tech. 91 (3), 228–239. http://dx.doi.org/10.1002/cite.201800091.

McDonald, M.A., Bommarius, A.S., Rousseau, R.W., Grover, M.A., 2019. Continuous reactive crystallization of β-lactam antibiotics catalyzed by penicillin G acylase. Part I: Model development. Comput. Chem. Eng. 123, 331–343. http://dx.doi.org/10.1016/j.compchemeng.2018.12.029.

Meng, Q., Anandan, P.D., Rielly, C.D., Benyahia, B., 2023. Multi-agent reinforcement learning and RL-based adaptive PID control of crystallization processes. In: Kokossis, A.C., Georgiadis, M.C., Pistikopoulos, E. (Eds.), 33rd European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 52, Elsevier, pp. 1667–1672. http://dx.doi.org/10.1016/B978-0-443-15274-0.50265-1.

Meyer, C., Arora, A., Scholl, S., 2024. A method for the rapid creation of AI driven crystallization process controllers. Comput. Chem. Eng. 186, 108680. http://dx.doi.org/10.1016/j.compchemeng.2024.108680.

Moraes, M.G.F., Lima, F.A.R.D., Lage, P.L.d.C., de Souza, M.B.J., Barreto, A.G.J., Secchi, A.R., 2023. Modeling and predictive control of cooling crystallization of potassium sulfate by dynamic image analysis: Exploring phenomenological and machine learning approaches. Ind. Eng. Chem. Res. 62 (24), 9515–9532. http://dx.doi.org/10.1021/acs.iecr.3c00739.

Morris, G., Power, G., Ferguson, S., Barrett, M., Hou, G., Glennon, B., 2015. Estimation of nucleation and growth kinetics of benzoic acid by population balance modeling of a continuous cooling mixed suspension, mixed product removal crystallizer. Org. Process Res. Dev. 19 (12), 1891–1902. http://dx.doi.org/10.1021/acs.oprd.5b00139, URL: https://pubs.acs.org/doi/10.1021/acs.oprd.5b00139.

Nagy, Z.K., Braatz, R.D., 2003. Robust nonlinear model predictive control of batch processes. AIChE J. 49 (7), 1776–1786. http://dx.doi.org/10.1002/aic.690490715.

Nagy, Z.K., Braatz, R.D., 2012. Advances and new directions in crystallization control. Annu. Rev. Chem. Biomol. Eng. 3 (1), 55–75. http://dx.doi.org/10.1146/annurev-chembioeng-062011-081043.

Nagy, Z.K., Chew, J.W., Fujiwara, M., Braatz, R.D., 2004. Advances in the modeling and control of batch crystallizers. IFAC Proc. Vol. 37 (1), 83–90. http://dx.doi.org/10.1016/s1474-6670(17)38713-x.

Nagy, Z., Fujiwara, M., Braatz, R., 2008a. Modelling and control of combined cooling and antisolvent crystallization processes. J. Process Control 18 (9), 856–864. http://dx.doi.org/10.1016/j.jprocont.2008.06.002, Selected Papers From Two Joint Conferences: 8th International Symposium on Dynamics and Control of Process Systems and the 10th Conference Applications in Biotechnology.

Nagy, Z.K., Fujiwara, M., Woo, X.Y., Braatz, R.D., 2008b. Determination of the kinetic parameters for the crystallization of paracetamol from water using metastable zone width experiments. Ind. Eng. Chem. Res. 47 (4), 1245–1252. http://dx.doi.org/10.1021/ie060637c.

Narayanan, H., Cruz Bournazou, M.N., Guillén Gosálbez, G., Butté, A., 2022. Functional-hybrid modeling through automated adaptive symbolic regression for interpretable mathematical expressions. Chem. Eng. J. 430, 133032. http://dx.doi.org/10.1016/j.cej.2021.133032.

Nian, R., Liu, J., Huang, B., 2020. A review on reinforcement learning: Introduction and applications in industrial process control. Comput. Chem. Eng. 139, 106886. http://dx.doi.org/10.1016/j.compchemeng.2020.106886.

Nielsen, R.F., Gernaey, K.V., Mansouri, S.S., 2020. A hybrid model predictive control strategy using neural network based soft sensors for particle processes. In: Pierucci, S., Manenti, F., Bozzano, G.L., Manca, D. (Eds.), 30th European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 48, Elsevier, pp. 1177–1182. http://dx.doi.org/10.1016/B978-0-12-823377-1.50197-X.

Nogueira, I.B.R., Santana, V.V., Ribeiro, A.M., Rodrigues, A.E., 2022. Using scientific machine learning to develop universal differential equation for multicomponent adsorption separation systems. Can. J. Chem. Eng. 100 (9), 2279–2290. http://dx.doi.org/10.1002/cjce.24495.

Nyande, B.W., Nagy, Z.K., Lakerveld, R., 2024. Data-driven identification of crystallization kinetics. AIChE J. 70 (5), e18333. http://dx.doi.org/10.1002/aic.18333.

O'Ciardhá, C.T., Mitchell, N.A., Hutton, K.W., Frawley, P.J., 2012. Determination of the crystal growth rate of paracetamol as a function of solvent composition. Ind. Eng. Chem. Res. 51 (12), 4731–4740. http://dx.doi.org/10.1021/ie2020262.

Ojha, V.K., Abraham, A., Snášel, V., 2017. Metaheuristic design of feedforward neural networks: A review of two decades of research. Eng. Appl. Artif. Intell. 60, 97–116. http://dx.doi.org/10.1016/j.engappai.2017.01.013.

Oliveira, C., Georgieva, P., Rocha, F., Feyo de Azevedo, S., 2009. Artificial neural networks for modeling in reaction process systems. Neural Comput. Appl. 18, 15–24. http://dx.doi.org/10.1007/s00521-008-0200-8.

Oner, M., Montes, F.C., ahlberg, T.S., Stocks, S.M., Bajtner, J.E., Sin, G., 2020. Comprehensive evaluation of a data driven control strategy: Experimental application to a pharmaceutical crystallization process. Chem. Eng. Res. Des. 163, 248–261. http://dx.doi.org/10.1016/j.cherd.2020.08.032.

Perkett, M.R., Hagan, M.F., 2014. Using Markov state models to study self-assembly. J. Chem. Phys. 140 (21), http://dx.doi.org/10.1063/1.4878494.

Petsagkourakis, P., Sandoval, I., Bradford, E., Zhang, D., del Rio-Chanona, E., 2020. Reinforcement learning for batch bioprocess optimization. Comput. Chem. Eng. 133, 106649. http://dx.doi.org/10.1016/j.compchemeng.2019.106649.

Pham, B.T., Nguyen-Thoi, T., Qi, C., Phong, T.V., Dou, J., Ho, L.S., Le, H.V., Prakash, I., 2020. Coupling RBF neural network with ensemble learning techniques for landslide susceptibility mapping. Catena 195, 104805. http://dx.doi.org/10.1016/j.catena.2020.104805.

Psichogios, D.C., Ungar, L.H., 1991. Direct and indirect model based control using artificial neural networks. Ind. Eng. Chem. Res. 30 (12), 2564–2573. http://dx.doi.org/10.1021/ie00060a009.

Quilló, G.L., Bhonsale, S., Gielen, B., Van Impe, J.F., Collas, A., Xiouras, C., 2021. Crystal growth kinetics of an industrial active pharmaceutical ingredient: Implications of different representations of supersaturation and simultaneous growth mechanisms. Cryst. Growth Des. 21 (9), 5403–5420. http://dx.doi.org/10.1021/acs.cgd.1c00677.

Rackauckas, C., Ma, Y., Martensen, J., Warner, C., Zubov, K., Supekar, R., Skinner, D., Ramadhan, A., Edelman, A., 2020. Universal differential equations for scientific machine learning. pp. 1–55. http://dx.doi.org/10.48550/arXiv.2001.04385.

Ren, J., Ni, D., 2020. A batch-wise LSTM-encoder decoder network for batch process monitoring. Chem. Eng. Res. Des. 164, 102–112. http://dx.doi.org/10.1016/j.cherd.2020.09.019.

Rohani, S., Haeri, M., Wood, H., 1999. Modeling and control of a continuous crystallization process Part 2. Model predictive control. Comput. Chem. Eng. 23 (3), 279–286. http://dx.doi.org/10.1016/S0098-1354(98)00272-5.

Romdhani, A., Martínez, F., Almanza, O.A., Jouyban, A., Acree, W.E., 2020. Solubility of acetaminophen in (ethanol + propylene glycol + water) mixtures: Measurement, correlation, thermodynamics, and volumetric contribution at saturation. J. Mol. Liq. 318, 114065. http://dx.doi.org/10.1016/j.molliq.2020.114065.

Salami, H., McDonald, M.A., Bommarius, A.S., Rousseau, R.W., Grover, M.A., 2021. In situ imaging combined with deep learning for crystallization process monitoring: Application to cephalexin production. Org. Process Res. Dev. 25 (7), 1670–1679. http://dx.doi.org/10.1021/acs.oprd.1c00136.

Saleemi, A., Rielly, C., Nagy, Z., 2012. Monitoring of the combined cooling and anti-solvent crystallisation of mixtures of aminobenzoic acid isomers using ATR-UV/vis spectroscopy and FBRM. Chem. Eng. Sci. 77, 122–129. http://dx.doi.org/10.1016/j.ces.2012.02.005, 18th International Symposium on Industrial Crystallization.

Santana, V.V., Gama, M.S., Loureiro, J.M., Rodrigues, A.E., Ribeiro, A.M., Tavares, F.W., Barreto, A.G., Nogueira, I.B.R., 2022. A first approach towards adsorption-oriented physics-informed neural networks: Monoclonal antibody adsorption performance on an ion-exchange column as a case study. ChemEngineering 6 (2), http://dx.doi.org/10.3390/chemengineering6020021.

Scheffold, L., Finkler, T., Piechottka, U., 2021. Gray-box system modeling using symbolic regression and nonlinear model predictive control of a semibatch polymerization. Comput. Chem. Eng. 146, 107204. http://dx.doi.org/10.1016/j.compchemeng.2020.107204.

Shahnazari, H., 2020. Fault diagnosis of nonlinear systems using recurrent neural networks. Chem. Eng. Res. Des. 153, 233–245. http://dx.doi.org/10.1016/j.cherd.2019.09.026.

Sharma, N., Liu, Y.A., 2022. A hybrid science-guided machine learning approach for modeling chemical processes: A review. AIChE J. 68 (5), e17609. http://dx.doi.org/10.1002/aic.17609.

Sheikhzadeh, M., Trifkovic, M., Rohani, S., 2008. Adaptive MIMO neuro-fuzzy logic control of a seeded and an unseeded anti-solvent semi-batch crystallizer. Chem. Eng. Sci. 63 (5), 1261–1272. http://dx.doi.org/10.1016/j.ces.2007.07.022, Control of Particulate Processes.

Shin, J., Badgwell, T.A., Liu, K.-H., Lee, J.H., 2019. Reinforcement learning – Overview of recent progress and implications for process control. Comput. Chem. Eng. 127, 282–294. http://dx.doi.org/10.1016/j.compchemeng.2019.05.029.

Silvestri, M., Baldo, F., Misino, E., Lombardi, M., 2023. An analysis of universal differential equations for data-driven discovery of ordinary differential equations. In: Mikyška, J., de Mulatier, C., Paszynski, M., Krzhizhanovskaya, V.V., Dongarra, J.J., Sloot, P.M. (Eds.), Computational Science – ICCS 2023. Springer Nature Switzerland, Cham, pp. 353–366.

Sirohi, D., Kumar, N., Rana, P.S., 2020. Convolutional neural networks for 5G-enabled intelligent transportation system : A systematic review. Comput. Commun. 153, 459–498. http://dx.doi.org/10.1016/j.comcom.2020.01.058.

Sitapure, N., Kwon, J.S.-I., 2023a. Crystalgpt: Enhancing system-to-system transferability in crystallization prediction and control using time-series-transformers. Comput. Chem. Eng. 177, 108339. http://dx.doi.org/10.1016/j.compchemeng.2023.108339.

Sitapure, N., Kwon, J.S.-I., 2023b. Exploring the potential of time-series transformers for process modeling and control in chemical systems: An inevitable paradigm shift? Chem. Eng. Res. Des. 194, 461–477. http://dx.doi.org/10.1016/j.cherd.2023.04.028.

Sitapure, N., Kwon, J.S.-I., 2023c. Introducing hybrid modeling with time-series-transformers: A comparative study of series and parallel approach in batch crystallization. Ind. Eng. Chem. Res. 62 (49), 21278–21291. http://dx.doi.org/10.1021/acs.iecr.3c02624.

Sitapure, N., Kwon, J.S.-I., 2024. Machine learning meets process control: Unveiling the potential of LSTMc. AIChE J. 70 (7), e18356. http://dx.doi.org/10.1002/aic.18356.

Sun, F., Liu, T., Song, B., Cui, Y., Nagy, Z.K., Findeisen, R., 2024. Multi-objective optimization based nonlinear model predictive control of seeded cooling crystallization process with application to β form L-glutamic acid. Chem. Eng. Sci. 299, 120475. http://dx.doi.org/10.1016/j.ces.2024.120475.

Sutton, R.S., Barto, A.G., 2018. Reinforcement Learning: An Introduction. MIT Press.

Szilágyi, B., Eren, A., Quon, J.L., Papageorgiou, C.D., Nagy, Z.K., 2022. Digital design of the crystallization of an active pharmaceutical ingredient using a population balance model with a novel size dependent growth rate expression. From development of a digital twin to in silico optimization and experimental validation. Cryst. Growth Des. 22 (1), 497–512. http://dx.doi.org/10.1021/acs.cgd.1c01108.

Szilágyi, B., Nagy, Z.K., 2018. Aspect ratio distribution and chord length distribution driven modeling of crystallization of two-dimensional crystals for real-time model-based applications. Cryst. Growth Des. 18 (9), 5311–5321. http://dx.doi.org/10.1021/acs.cgd.8b00758.

Szilagyi, B., Nagy, Z.K., 2019. Real-time feasible model-based crystal size and shape control of crystallization processes. In: Kiss, A.A., Zondervan, E., Lakerveld, R., Özkan, L. (Eds.), 29th European Symposium on Computer Aided Process Engineering. In: Computer Aided Chemical Engineering, vol. 46, Elsevier, pp. 1273–1278. http://dx.doi.org/10.1016/B978-0-12-818634-3.50213-7.

Tang, X., Bevan, M.A., Grover, M.A., 2017. The construction and application of Markov state models for colloidal self-assembly process control. Mol. Syst. Des. Eng. 2 (1), 78–88. http://dx.doi.org/10.1039/C6ME00092D.

Tang, W., Quan, Y., Gong, J., Wang, J., Yin, Q., Li, T., 2021. Form selection of concomitant polymorphs: A case study informed by crystallization kinetics modeling. AIChE J. 67 (4), e17129. http://dx.doi.org/10.1002/aic.17129.

Temmel, E., Gänsch, J., Lorenz, H., Seidel-Morgenstern, A., 2018. Measurement and evaluation of the crystallization kinetics of l -asparagine monohydrate in the ternary l -/ d -asparagine/water system. Cryst. Growth Des. 18 (12), 7504–7517. http://dx.doi.org/10.1021/acs.cgd.8b01322, URL: https://pubs.acs.org/doi/10.1021/acs.cgd.8b01322.

Vasanth Kumar, K., Martins, P., Rocha, F., 2008. Modelling of the batch sucrose crystallization kinetics using artificial neural networks: Comparison with conventional regression analysis. Ind. Eng. Chem. Res. 47 (14), 4917–4923. http://dx.doi.org/10.1021/ie701706v.

Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A.N., Kaiser, L.u., Polosukhin, I., 2017. Attention is all you need. In: Guyon, I., Luxburg, U.V., Bengio, S., Wallach, H., Fergus, R., Vishwanathan, S., Garnett, R. (Eds.), Advances in Neural Information Processing Systems. Vol. 30, Curran Associates, Inc., URL: https://proceedings.neurips.cc/paper_files/paper/2017/file/3f5ee243547dee91fbd053c1c4a845aa-Paper.pdf.

Vogel, G., Schulze Balhorn, L., Schweidtmann, A.M., 2023. Learning from flowsheets: A generative transformer model for autocompletion of flowsheets. Comput. Chem. Eng. 171, 108162. http://dx.doi.org/10.1016/j.compchemeng.2023.108162.

Wang, Y., Wagner, N., Rondinelli, J.M., 2019. Symbolic regression in materials science. MRS Commun. 9 (3), 793–805. http://dx.doi.org/10.1557/mrc.2019.85.

Wang, L., Zhu, Y., 2022. Neural-network-based nonlinear model predictive control of multiscale crystallization process. Processes 10 (11), http://dx.doi.org/10.3390/pr10112374.

Wang, L., Zhu, Y., Gan, C., 2022. Predictive control of particlesize distribution of crystallization process using deep learning based image analysis. AIChE J. 68 (11), e17817. http://dx.doi.org/10.1002/aic.17817.

Woinaroschy, A., Isopescu, R., Filipescu, L., 1994. Crystallization process optimization using artificial neural networks. Chem. Eng. Technol. 17 (4), 269–272. http://dx.doi.org/10.1002/ceat.270170408.

Worlitschek, J., Mazzotti, M., 2004. Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol. Cryst. Growth Des. 4 (5), 891–903. http://dx.doi.org/10.1021/cg034179b, arXiv:https://doi.org/10.1021/cg034179b.

Wu, G., Wu, Z., 2023. Machine learning-based MPC of batch crystallization process using physics-informed RNNs. IFAC-PapersOnLine 56 (2), 2846–2851. http://dx.doi.org/10.1016/j.ifacol.2023.10.1399, URL: https://www.sciencedirect.com/science/article/pii/S2405896323018074, 22nd IFAC World Congress.

Wu, G., Yion, W.T.G., Dang, K.L.N.Q., Wu, Z., 2023a. Physics-informed machine learning for MPC: Application to a batch crystallization process. Chem. Eng. Res. Des. 192, 556–569. http://dx.doi.org/10.1016/j.cherd.2023.02.048.

Wu, L., Zhang, S., Chen, W., Hao, X., 2023b. Identification and correction of abnormal measurement data in power system based on graph convolutional network and gated recurrent unit. Electr. Power Syst. Res. 224, 109740. http://dx.doi.org/10.1016/j.epsr.2023.109740.

Xiouras, C., Cameli, F., Quilló, G.L., Kavousanakis, M.E., Vlachos, D.G., Stefanidis, G.D., 2022. Applications of artificial intelligence and machine learning algorithms to crystallization. Chem. Rev. 122 (15), 13006–13042. http://dx.doi.org/10.1021/acs.chemrev.2c00141.

Yu, L., Lai, K.K., Wang, S., 2008. Multistage RBF neural network ensemble learning for exchange rates forecasting. Neurocomputing 71 (16), 3295–3302. http://dx.doi.org/10.1016/j.neucom.2008.04.029, Advances in Neural Information Processing (ICONIP 2006) / Brazilian Symposium on Neural Networks (SBRN 2006).

Zendehboudi, S., Rezaei, N., Lohi, A., 2018. Applications of hybrid models in chemical, petroleum, and energy systems: A systematic review. Appl. Energy 228, 2539–2566. http://dx.doi.org/10.1016/j.apenergy.2018.06.051.

Zhang, W., Ni, P., Zhao, M., Du, X., 2024. A general method for solving differential equations of motion using physics-informed neural networks. Appl. Sci. 14 (17), http://dx.doi.org/10.3390/app14177694.

Zhang, J., Yang, J., Zhang, Y., Bevan, M.A., 2020. Controlling colloidal crystals via morphing energy landscapes and reinforcement learning. Sci. Adv. 6 (48), eabd6716. http://dx.doi.org/10.1126/sciadv.abd6716.

Zheng, Y., Wang, X., Wu, Z., 2022a. Machine learning modeling and predictive control of the batch crystallization process. Ind. Eng. Chem. Res. 61 (16), 5578–5592. http://dx.doi.org/10.1021/acs.iecr.2c00026.

Zheng, Y., Wu, Z., 2022a. Online learning for machine learning-based modeling and predictive control of crystallization processes under batch-to-batch parametric drift. In: 2022 IEEE International Symposium on Advanced Control of Industrial Processes. AdCONIP, pp. 216–221. http://dx.doi.org/10.1109/AdCONIP55568.2022.9894157.

Zheng, Y., Wu, Z., 2022b. Predictive control of batch crystallization process using machine learning. IFAC-PapersOnLine 55 (7), 798–803. http://dx.doi.org/10.1016/j.ifacol.2022.07.542, 13th IFAC Symposium on Dynamics and Control of Process Systems, including Biosystems DYCOPS 2022.

Zheng, Y., Zhao, T., Wang, X., Wu, Z., 2022b. Online learning-based predictive control of crystallization processes under batch-to-batch parametric drift. AIChE J. 68 (11), e17815. http://dx.doi.org/10.1002/aic.17815.