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Modeling and control of crystal shape in continuous protein crystallization

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HIGHLIGHTS

- Kinetic Monte Carlo simulation of protein crystal growth.
- Approximate model for evolution of protein crystal shape in continuous crystallization.
- Model predictive control of protein crystal shape in a continuous crystallizer.
- Disturbance handling using model predictive control.

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ABSTRACT

In this work, a continuous crystallization process with a fines trap is modeled in an effort to produce tetragonal hen-egg-white (HEW) lysozyme crystals with a desired shape distribution. The crystal shape of tetragonal lysozyme crystals is defined by the aspect ratio of the crystal heights in the direction of the (110) and (101) faces. A kinetic Monte Carlo (kMC) simulation is used to model the crystal nucleation, growth, and dissolution through a fines trap in a continuous crystallization process. Specifically, the crystal growth processes are simulated through adsorption, desorption, and migration mechanisms, and the crystal growth rates are calibrated through experimental data (Durbin and Feher, 1986). Additionally, a nucleation rate expression is developed based on the results from an experimental work (Galkin and Vekilov, 2001) to simulate the crystals nucleated at different times. Then, the method of moments is used to approximate the dominant behavior of a population balance equation (PBE) describing the evolution of the crystal volume distribution through the three leading moments. The moment model is used, along with solute mass and energy balance equations, to design a model predictive controller (MPC), which allows for the crystallizer to produce crystals with a desired shape distribution. In the proposed MPC, the jacket temperature is manipulated to appropriately suppress the influence of undesired effects such as process disturbances and measurement noise, while handling significant changes in the set-point value. Furthermore, it is demonstrated that a continuous process with a fines trap can produce crystals with a low polydispersity.

1. Introduction

Protein crystallization is essential in the context of separation and purification processes in the pharmaceutical industry. More than 90% of all active pharmaceutical ingredients (API) are in the crystalline form of organic compounds. Depending on the final dosage form (e.g., tablet, capsule, liquids, syrups, creams and injections), the production of API crystals with desired size and shape distributions is required for bioavailability and stability of the final dosage forms, because size and shape distributions significantly influence the physical properties of the crystalline APIs (e.g., dissolution rates in the blood and melting points). In particular, when the products are off the desired specification, additional downstream processes (e.g., filtration, drying, and granulation) are needed. Therefore, the modeling of the crystallization process in an effort to control the size and shape distributions of crystals produced from the system is necessary to facilitate the further development of pharmaceutical processes.

Over the last few decades, batch processes have received dominant attention in the pharmaceutical industry. In batch

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operations, a drug's APIs are synthesized and then carried to other facilities where they are turned into a large amount of a desired final dosage form. Although the research and development period plays a major role in the time-to-market, the inefficiency owing to the distant nature of facilities involved in the crystallization processes will cause additional delay in the time-to-market and it will be handled through a series of continuous crystallizers. Additionally, due to the nature of a batch process, there are a number of issues that need to be addressed such as batch-to-batch variability, high equipment and operational costs, and relatively long separation time of the APIs (Lawton et al., 2009).

Recently, continuous crystallization, which is able to consistently produce crystals with desired size and shape distributions starting from fresh raw materials, is receiving growing attention in the pharmaceutical industry. Specifically, once a steady-state has been achieved in a continuous crystallizer, all crystals are produced under a uniform supersaturation level, which leads to greater reproducibility and controllability of major characteristics of crystals such as size and shape distributions. As a result, the number of downstream operations required to amend crystals with undesired size and shape distributions (e.g., granulation for the solid dosage forms) may be reduced.

Consequently, using a continuous manufacturing process can stimulate the growth of the pharmaceutical industry as it may reduce the size of production facilities, operating costs, waste, energy consumption, and raw material usage considerably. Moreover, the reproducibility and controllability of the APIs in the final dosage form can be improved.

Motivated by above, researchers have made notable advancements in the context of fundamental understanding and modeling of protein crystallization for crystal nucleation (Galkin and Vekilov, 1999; Pusey and Nadarajah, 2002) and crystal growth (Durbin and Feher, 1986; Forsythe et al., 1999; Kurihara et al., 1996). Specifically, kinetic Monte Carlo simulation methods (kMC) (Bortz et al., 1975; Dai et al., 2005, 2008; Gillespie, 1976, 1977, 1978, 1992, 2001, 2007; Rathinam et al., 2003; Reese et al., 2001; Snyder et al., 2005) have been widely applied to simulate crystal growth including the previous work of our group (Nayhouse et al., 2013, Kwon et al., 2013a, 2013b, in press) where we modeled crystal growth in batch processes. In the present work, the kMC methodology is further developed to model a continuous protein crystallization process, and implemented in the way described in Christofides et al. (2008) using the rate equations on the crystal surface reaction initially developed by Durbin and Feher (1991).

Then, a population balance model for a continuous crystallization process with a fines trap is presented. In practice, the complexity in a population balance model usually leads to an implementation issue with the controller design (Chiu and Christofides, 1999). Therefore, the method of moments is used to derive reduced-order ordinary differential equation (ODE) models in time, which are used to approximate the dominant behavior of the evolution of crystal volume distribution in a continuous crystallizer (El-Farra et al., 2001; Kalani and Christofides, 2002). In order to close the moment model, a normal distribution assumption is used to approximate the crystal volume distribution. In addition to a set of polynomials that describes the dependence of crystal growth of each face on a supersaturation level, the mass and energy balance equations and the moment models are considered to design a model predictive control (MPC) system, which is used to produce crystals with a desired shape distribution. To improve the controller performance, an advanced real-time monitoring technique is necessary in practice, because the damage is irreversible if the produced crystals are off the desired specification at the outlet of the process. Motivated by this, the measurements of crystals through the use of focused beam reflectance measurement (FBRM) and process vision and measurement (PVM) (Kougoulos et al., 2005) are modeled as measurement system feedback in real time from the kMC simulations, which is treated as the physical crystallization process.

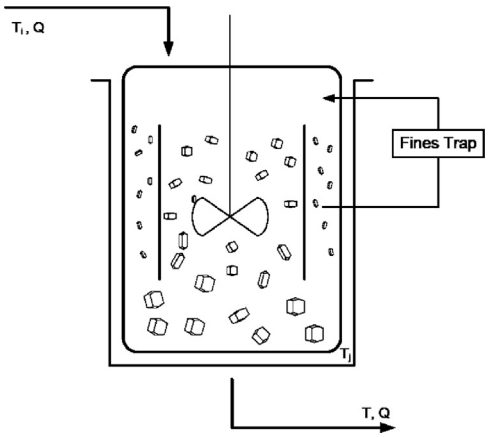

Fig. 1. MSMPR crystallizer used in this work.

The manuscript is organized as follows. First, we will introduce a continuous crystallization process with a fines trap. Then, the crystallizer rate equations used for the implementation of the kMC simulation method will be introduced. Next, a set of mass and energy balances will be presented along with a PBM of the crystal volume distribution, and the method of moment will be used to construct a reduced-order model for the design of a model predictive controller, which will drive the shape distribution of crystal population to a desired value. Finally, we will finish with closed-loop simulation results under the proposed MPC, followed by a short conclusion.

2. Process descriptions

2.1. Continuous crystallizers

There are two types of the most widely used continuous crystallizers in the pharmaceutical industry: mixed suspension mixed product removal (MSMPR) and plug flow reactors (PFR). The choice of which to use is mainly determined by the characteristics of the process, as MSMPR is generally preferred for low conversions and longer residence times, while PFR is preferred for higher conversions with shorter residence times. In general, MSMPR is preferred because it is relatively similar to the conventional batch process (Chen et al., 2011).

The low conversion in MSMPR can be improved by strategies such as the addition of a recycle stream or the addition of a fines trap. More specifically, an increase in yield was observed by Alvarez et al. (2011) and Wong et al. (2012) through the implementation of recycle streams to MSMPR systems for the crystallization of cyclosporine. Additionally, it was demonstrated that the multistage MSMPR approach was simplified into a single-stage MSMPR by implementing a recycle stream and a fines trap (Griffin et al., 2010).

A fines trap is one of the most widely used product classification processes, and it can be established, first of all, by shielding a part of a mixed crystallizer with a baffle as is shown in Fig. 1. As a result, the circulation of the continuous phase through the baffled region is typically slow, and larger crystals sink to the bottom of crystallizer while small crystal fines float on the top where a stream is drawn off and sent to the fines trap where small crystals are dissolved and are recycled back to the crystallizer. By manipulating the stirrer speed in the baffled continuous crystallizer, we can control the maximum particle size L_{max} that will enter the