Concentration Control for Semi-batch pH-shift Reactive Crystallization of L-glutamic Acid

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Abstract: While major advances have been made in the control of cooling and antisolvent crystallizations, very little progress has been made for the much more challenging pH-shift reactive crystallizations that are also quite common in industry. This paper extends the concentration control strategy developed for cooling and antisolvent crystallization to pH-shift reactive crystallization of L-glutamic acid. The straightforward extension to semi-batch pH-shift reactive crystallization is not applicable, which motivates a variant that incorporates data-based models so as to better cope with process nonlinearity. Further analysis motivates the development of control strategies that directly incorporate measurements of the key product quality attributes.

1. INTRODUCTION

The prevalence and high value of crystallization processes in the pharmaceutical, fine chemical, and food industries have motivated the development of many control strategies (e.g., see Rawlings et al., 1993; Braatz, 2002; Fevotte, 2002; Fujiwara et al., 2005; Yu et al., 2004; Nagy and Braatz, 2012; and references cited therein). The solute concentration is a critical state variable to control during a crystallization, as the crystallization kinetics are usually written in terms of the supersaturation written as the difference between the solute concentration and saturated concentration.

A control strategy for batch and semibatch crystallizations that has become popular in recent years is to determine an optimal solute concentration or supersaturation trajectory as a function of other system states throughout the run, and then design a feedback control system to maintain the optimal relationship between the states (Zhou et al., 2006; Nagy et al., 2008). Detailed uncertainty and disturbance analyses carried out both experimentally and in simulations have shown that the approach ensures the consistent production of large crystals by suppressing excessive nucleation and the formation of undesired polymorphs (Kee et al., 2009a, 2009b). This so-called concentration control (C-control) approach, in which the trajectories of concentration vs. temperature or concentration vs. antisolvent mass fraction are tracked throughout the run, has been implemented in many cooling and antisolvent crystallizations (e.g., Zhou et al., 2006; Nagy et al., 2008; Cote et al., 2009; Kee et al., 2009a, 2009b).

However, pH-shift reactive crystallization processes are also common in industrial practice and are more challenging to control as discussed later in this paper. This lack of effective control strategies motivates this paper to extend the C-control strategy to a pH-shift reactive crystallization using L-glutamic acid as a model compound.

2. CONVENTIONAL C-CONTROL STRATEGY

Two methods for implementing C-control have been employed in cooling crystallization with main difference in the choice of set point for a lower-level PID control loop, i.e., concentration set point (Nagy et al., 2008) or temperature set point (Zhou et al., 2006). It has been argued that the control tuning is more difficult for the former, particularly for complicated crystallization systems (Alatalo et al., 2010), so this paper considers only the latter approach.

For illustration purposes, the implementation of C-control for batch cooling crystallization (Zhou et al., 2006) is schematically shown in Fig. 1, where the solid curve represents the desired concentration vs. temperature trajectory tracked by the C-control within the batch. Suppose the process is at system state A with solute concentration \( C(k) \) and temperature \( T(k) \), where a deviation from the target trajectory is observed. The C-control implementation determines the new set point \( T^\text{set}(k) \) for the temperature controller by drawing a horizontal line from point A that intersects with the target trajectory at point B, which in turns specifies \( T^\text{set}(k) \). Even if the lower-level PID temperature controller could adjust the crystallizer’s temperature to the new set point in one sampling instant, i.e., \( T(k+1) = T^\text{set}(k) \), this will not force the process to reach point B, because the solute concentration will decrease during the sampling interval. This decrease in the solute concentration from \( C(k) \) to \( C(k+1) \) results in the state moving from A to C in Fig. 1. Repeating the procedure of A→B→C, the desired trajectory can be tracked fairly closely, provided that the deviation of B to C is small, which occurs when the crystallization kinetics are slow within one sampling interval. This strategy can be similarly applied to antisolvent crystallization by replacing the concentration vs. temperature trajectory by a concentration vs. antisolvent mass fraction trajectory (Zhou et al., 2006), and taking into account the dilution effect (Woo et al., 2009).
The conventional C-control neglects the crystallization effect on the solution concentration by simply treating the solute concentration as being constant when the solution is cooled from $T(k)$ to $T_{\text{set}}(k)$, i.e., $\dot{C}(k + 1) = C(k)$, as shown by the line A→B in Fig. 1. Advantages of this approach are that estimation of the crystallization kinetics is not required, and it is also conservative as it cannot overshoot the desired trajectory given that the solubility curve is monotonic. However, the overall batch time is increased, which lowers the productivity of the equipment (Nagy et al., 2008). An alternative approach is to utilize a process model to predict the effect of crystallization on the solute concentration while determining the set point $T'_{\text{set}}(k)$, as shown by the dashed line of A→D, where at point D the model prediction $\dot{C}(k + 1')$ intersects the desired trajectory. In doing so, a larger temperature decrease from $T(k)$ to $T'_{\text{set}}(k)$ is made compared to moving from $T(k)$ to $T_{\text{set}}(k)$. This reduces the overall batch time, but raises the possibility of overshooting the desired trajectory if the process model has uncertainties.

The conventional C-control in both cooling and antisolvent crystallization relies on the fact that solute concentration trajectory is usually monotonically decreasing as shown in Fig. 1, as well as the assumption of slow crystallization kinetics within a sampling time. However, its performance may become too sluggish when applied to a reactive crystallization that can switch from very slow to very fast crystallization rates and/or with a dome-shaped solute concentration trajectory, as shown in Fig. 2 for a semi-batch pH-shift reactive crystallization (Borissova et al., 2005; Alatalo et al., 2008; Qu et al., 2009), where supersaturation varies considerably during the batch. To overcome the challenging process characteristics inherent in reactive pH-shift crystallization that constrain the best achievable performance of C-control, the objective of this study is to propose special provision in order to enhance the performance of conventional C-control strategy to better cope with the pH-shift reactive crystallization, which is detailed in the next section.

3. C-CONTROL FOR SEMI-BATCH PH-SHIFT REACTIVE CRYSTALLIZATION

In this study, a mathematical model developed from the published data (Alatalo et al., 2008; Qu et al., 2009) was used to simulate the semi-batch pH-shift reactive crystallization of L-glutamic acid, with model details not reported here due to space limitations. The crystallizer is initially filled with monosodium glutamate (MSG) of 1.0 mol/L, with the maximum allowable volume is 0.97 L, the default batch time is 40 min, and the sampling interval is 1 min. The manipulated variable is the addition flowrate of sulfuric acid (SA) of 1.0 mol/L, which is constrained between 0 and 16 ml/min while adjusted every minute to achieve the maximum polymorphic purity of α-form, mean crystal size, and product yield of the final crystalline product at the batch end. The pareto-optimality front for this multi-objective optimization is shown in Fig. 3, which was solved using the Non-dominated Sorting Genetic Algorithm-II (NSGA-II) (Deb et al., 2002). The chosen optimal operating point is denoted by the star symbol in Fig. 3 and the corresponding optimal state trajectories are shown in Figs. 4 and 5.

In addition to the varying supersaturation profile mentioned above, it is evident from Fig. 2 that this process exhibits strong nonlinearity by observing the reverse in the sign of process gain at two sampling instants $k$ and $m$, which inherently limits the performance of the conventional C-control strategy in tracking the pre-specified target trajectory. To address these challenging process dynamics, the data-based local modeling technique based on the Just-in-Time Learning (JITL) modeling methodology (Cheng and Chiu, 2004) is used to improve the performance of conventional C-control. In the proposed design, the solute concentration is predicted by the JITL method using the autoregressive exogenous (ARX) model:

$$C(k + 1) = \alpha_1 C(k) + \beta_1 V(k) + \beta_2 V(k + 1).$$

(1)

![Fig. 1. Implementation of C-control for a batch cooling crystallization.](image1)

![Fig. 2. The desired concentration vs. volume trajectory for C-control of a semi-batch pH reactive crystallization under isothermal operation.](image2)
The JITL-based C-control for the semi-batch pH-shift reactive crystallization is implemented in the following steps:

1. At sampling instant \( k \), both \( C(k) \) and \( V(k) \) are measured;
2. For a chosen value of \( V^{\text{set}}(k) \), the volume at the \( k+1 \) sampling instant is set as \( \bar{V}(k + 1) = V^{\text{set}}(k) \);
3. The predicted concentration at the \( k+1 \) sampling instant, \( \hat{C}(k + 1) \), is obtained by the JITL method using query data \( q = [C(k), V(k), \bar{V}(k + 1)] \); while the solute concentration \( \hat{C}(k + 1) \) corresponding to \( \bar{V}(k + 1) \) in the target trajectory is obtained from Fig. 4(c);
4. By comparing \( \hat{C}(k + 1) \) and \( \hat{C}(k + 1) \), the bisection method is used to update \( V^{\text{set}}(k) \) subject to constraints incurred by the minimum and maximum flowrates;
5. Steps 2 to 4 are repeated until \( V^{\text{set}}(k) \) converges or the maximum iteration number is reached, and the corresponding \( V^{\text{set}}(k) \) serves as the set point for the lower-level PID controller.

### Fig. 3. Pareto-optimality front obtained for a semi-batch pH-shift reactive crystallization.

### Fig. 4. Optimal (a) volume and (b) solute concentration profiles, and (c) corresponding target trajectory used for C-control.

### Fig. 5. Evolution of the three performance indices starting from \((0, 0, 0)\) during the batch.

### 4. RESULTS AND DISCUSSION

To proceed to the proposed C-control strategy, a reference database for the JITL method was generated using fifty batches process data by perturbing optimal flowrate profile corresponding to the optimal volume profile given in Fig. 4(a) with a normal distribution of \( N(0,1.0) \) at each sampling instant and varying initial concentrations of monosodium glutamate and sulfuric acid with \( N(0,0.02) \) for each batch. The resulting concentration data used to construct reference database are shown in Fig. 6. To evaluate the prediction accuracy of the JITL method, ten additional batches of process data were used in the validation test. The JITL method gave excellent prediction of the solute concentration, as the predicted outputs are almost indistinguishable with the actual solute concentration measurements (see Fig. 7).

To evaluate the robustness of the proposed JITL-based C-control strategy, uncertainties in the kinetics of crystal growth and nucleation of the polymorphic crystallization system, i.e., \( \alpha \)- and \( \beta \)-form polymorphs of L-glutamic acid, are considered. For the purpose of comparison, the flowrate control whose flowrate profile is determined by solving the optimal control problem for the nominal case is considered. The first case study considers 20% reduction of growth rate for the \( \alpha \)-form and Fig. 8 shows that the proposed C-control strategy provides much better tracking performance of the desired concentration vs. volume trajectory than the flowrate control. The improvement in the three performance indices obtained by using the proposed C-control is shown in Fig. 9 and Table 1. The corresponding flowrate profiles of these two control strategies are shown in Fig. 10.

The above results are in sharp contrast to both cooling and antisolvent crystallization processes, where C-control strategy has produced robust performance. The degraded performance of C-control in this particular pH-shift crystallization process is because the glutamic acid concentration is affected by competing polymorphic crystallizations and the relative rates of these competing processes cannot be observed by measuring only the glutamic
acid concentration. For example, the stable $\beta$-form polymorph can consume the solute at the expense of the $\alpha$-form that is less active than normal for a 20% decrease in crystal growth rate. However, in contrast, applications of conventional C-control to the cooling and antisolvent crystallization processes are operated under conditions where either the formation of alternative polymorphic forms is suppressed or only one polymorph can grow and the other polymorphs dissolve (Kee et al., 2009a, 2009b).

In summary, the proposed JITL-based C-control strategy is nearly as easy to implement as flowrate control while being more flexible and adaptive as it accelerated or decelerated the addition of sulfuric acid based on the solute concentration measurements. The JITL-based C-control was more robust in tracking the pre-defined concentration vs. volume trajectory than the flowrate control, with the performance improvement in the three key product quality indices ranging from significant (for a 20% reduction in growth rate) to modest (for 20% reduction in nucleation rate of the increase in sulfuric acid concentration).

5. CONCLUSIONS
This paper extends C-control to semibatch pH-shift reactive crystallization process by incorporating a data-based process model to better cope with the highly nonlinear dynamics inherent in this class of crystallization processes. Case studies are presented to evaluate the performance of proposed JITL-based C-control by considering its robustness against uncertainties in crystallization kinetics and sensitivity to concentration disturbances. Although the proposed JITL-based C-control is able to track the pre-specified concentration vs. volume trajectory closely, it did not necessarily result in better control performance in terms of final product measured by the three key product quality variables. The results suggest that good tracking of the concentration vs. volume trajectory alone may not be adequate for some cases. This motivates our future research to develop control strategies incorporating more relevant measurements that are directly linked to the product quality.
Fig. 9. Evolution of the three performance indices for a 20% reduction of growth rate for the α-form crystals.

Fig. 10. Flowrate trajectory for a 20% reduction of growth rate for the α-form crystals.

Fig. 11. Concentration vs. volume profiles obtained for a 20% reduction of nucleation rate for the α-form crystals.

Fig. 12. Evolution of the three performance indices for a 20% reduction of nucleation rate for the α-form crystals.

Fig. 13. Concentration-volume profiles obtained in the presence of disturbances in initial MSG and sulfuric acid feed concentrations.

REFERENCES


Table 1. Summary of the three case studies.

<table>
<thead>
<tr>
<th>Case study</th>
<th>Controller</th>
<th>Polymorphic purity</th>
<th>Mean crystal size, microns</th>
<th>Product yield</th>
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<tr>
<td>-20% growth rate for the α-form crystals</td>
<td>Flowrate control</td>
<td>0.707</td>
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<td>JITL-based C-control</td>
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<td>-20% nucleation rate for the α-form crystals</td>
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<td>0.793</td>
<td>247.389</td>
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<tr>
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<td>249.311</td>
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<tr>
<td>Excess sulfuric acid (MSG = 0.95, SA = 1.05)</td>
<td>Flowrate control</td>
<td>0.798</td>
<td>241.818</td>
<td>0.820</td>
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<tr>
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<td>JITL-based C-control</td>
<td>0.797</td>
<td>243.240</td>
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