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Reactive Crystallization Modeling for Process Integration Simulation

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ABSTRACT

Reactive crystallization (RC) is a chemical process in which the reaction yields a crystalline product. It is used in various industries such as pharmaceutical manufacturing or water purification. In some cases, RC is the only feasible process pathway, such as the precipitation of certain ionic solids from solution. In other cases, a reaction can become a RC by changing the reaction environment to a solvent with low product-solubility. Despite the utility and prevalence of RC, it is not often emphasized in process design software. There are RC models that simulate the inner reactions and dynamics of a RC, but each has limiting assumptions, and are difficult to integrate with the rest of a process-line simulation. This modeling gap complicates RC process design and limits the exploration of the possible benefits to using RC as well as the ability to optimize a system that relies on it. To fill this gap, we built an open-source, customizable model that can be integrated with other unit operations in the Python process simulator package PharmaPy. This model focuses on the reaction-crystallization interactions and dynamics to predict reaction yield and crystal critical quality attributes given inlet streams and reactor conditions. In this way, RC can be integrated with other unit operations to capture the effects RC has on the process overall. The model and assumptions are described in this work. The model space, limitations, and capabilities are explored. Finally, the potential benefits of the RC system are shown using three example cases.

Keywords: Process Intensification, Process Design, Crystallization, Reactive Crystallization

INTRODUCTION

Crystallization is a complex process highly relevant to numerous fields ranging from pharmaceuticals to agricultural chemicals [6]. It can be used to produce a solid product or simply as a separation technique for product purification. Reactive crystallization (RC) is the intensification of the crystallization process with the reaction that generates the crystallizing product.

The intensification of RC leads to multiple unique advantages. First, if the desired product exists in equilibrium with the reactants or a byproduct, or if the desired product is an intermediate species, RC provides a method for isolating the species away from the reaction. As solids are much more stable than liquid or gases, the crystallization renders the species effectively inert, pushing the reaction towards the crystallizing species due to Le Chatelier's principle thus increasing yield. Another advantage is a reduction of the process footprint. Because RC combines the tasks of a reactor with a crystallizer, a single unit is sufficient instead of the two in series. The final advantage of RC is the potential to remove a recrystallization/separation process if the produced crystals follow the desired critical quality attributes (CQAs).

Intensification comes at the cost of degrees of freedom, increasing the difficulty of control [8]. More difficult control may deter adoption of the technology and therefore must be balanced with the potential benefit [5, 8]. As such, it is necessary to design RC processes with control in mind. Most modern design techniques require the use of a digital model.

Modeling and predicting RC systems is notoriously difficult. Both reaction and crystallization dynamics are governed by concentration; this leads to highly coupled and inseparable numerical systems. Additionally, due to the system's general sensitivity to mixing effects, fluid dynamics are often considered as well. Salami et al. [7],

Tang et al. [9] are excellent examples of such approaches.

High resolution modeling of this nature can require more time to execute the simulation model than for the phenomenon to actually transpire. This prohibits the use of these types of models for real-time control or prediction. To address this problem, an open-source model is created which can simulate faster than real-time but it achieves this by neglecting mixing effects. The goal of this model, therefore, is to capture the overall behavior of the system even if the accuracy is lower than the high-resolution models mentioned. This model can then be customized to include other factors while potentially solving in real-time to be used in applications such as optimization and control.

METHODS

Mathematical Model

The RC system can be modeled using differential equations that capture the material and energy balances of the specific operations. A reactive mixed suspension, mixed product removal (RMSMPR) configuration was chosen as the target unit operation to model. This operation has the following assumptions:

1. All reactions only occur in the liquid/dissolved phase. Solids are inert.
2. Reactor volume is considered constant.
3. Agglomeration and breakage are negligible.
4. Crystal growth is size-independent and 1-dimensional.
5. Perfect mixing.
6. Total crystal volume is much smaller than the total reactor volume.

The material balance must include all inlet and outlet streams, as well as describe reactions and crystallization. The material balance used is given in equation 1. Here, equation 1 is written for the concentration c of each species j. In this system, ϵ is the liquid fraction, W_j is the amount of species j that crystallizes, q_k is the flow rate of each stream k, V is the volume of the reactor, and R_j is the reaction rate relevant to species j.

To capture crystallization behavior, a population balance was used and is shown in equation 2. Here, L_0 is the critical length required for the crystal to nucleate, and ρ_s is the density of the slurry. G and B are the growth rate and nucleation rate, respectively. L is the length of the crystal, n is the particle density function of the slurry, and n_k is the particle density function of the stream k, and δ is the dirac delta function. Equation 3 gives the nucleation and growth expressions. Here S is supersaturation, E is the activation energy for growth or nucleation, k_v is the shape factor and μ_3 is the third moment of the crystal size distribution (CSD). k_b, k_s, and k_g, follow the form in equation 4. k_0, b_1, s_1, s_2, g_1 are empirical parameters. R is the gas constant.

$$\frac{\partial \epsilon c_j V}{\partial t} = \sum_k c_{j,k}\, q_k \epsilon_k + V R_j + V \frac{dW_j}{dt} \quad (1)$$

$$\frac{\partial n(t,L)}{\partial t} + G\frac{\partial n(t,L)}{\partial L} = B \cdot \delta(L - L_0) + \sum_k \frac{q_k}{V} \cdot n_k \quad (2)$$

$$B = k_s S^{s_1} (k_v \mu_3)^{s_2} + k_b exp\left(\frac{-E_b}{RT}\right) S^{b_1} \quad (3a)$$

$$G = k_g exp\left(\frac{-E_g}{RT}\right) S^{g_1} \quad (3b)$$

$$k_x = k_0 exp\left(\frac{-E_a}{RT}\right) \quad (4)$$

Digital Implementation

PharmaPy is an open-source process simulator with a library of unit operations ranging from reactors and crystallizers to filters and dryers [2, 4]. The package is object oriented, using different classes to represent each unit operation. Instances of each unit operation can then be serially connected to create a flowsheet and solved sequentially to give the predicted behavior of the entire process.

PharmaPy reduces the partial differential equations to ordinary differential equations (ODEs) via the method of lines [2]. These ODEs are then solved using a numerical integrator. To solve the population balance, the one-dimensional finite volume method (FVM) is used. This method involves discretizing across the crystal length coordinate to create a balance for each length step. These equations are then solved using the CVode method from SUNDIALS [3], connected to python via the python package Assimulo [1].

An RC class was created following the PharmaPy syntax. Equations 1, 2 and 3 were used to describe the unit operation behavior, although the exact equations are easily modifiable if other effects such as agglomeration or breakage are desired. By following the PharmaPy layout, the RC class could be added into any flowsheet previously possible in PharmaPy. This flexibility allows the direct comparison of results between flowsheets using RC and those using reactors and crystallizers in series.

RESULTS

Using the PharmaPy RC model, several example systems were simulated. Each simulation generates outputs which include the predicted reaction profiles, dynamic CSDs, and temperature profiles. Figure 1 shows the crystallization information of the RC for the reaction system: A + B→ C↓ + D, where species C is crystallized as denoted by the downward arrow. The first five subplots (A-E) show the CSD against time in seconds. Figure 1F shows the liquid concentration of the target species, its solubility, and the absolute supersaturation. The parameters for this system are the same as case “A” given in Table 1, where k_r is the reaction rate constant and E_r is the reaction activation energy.

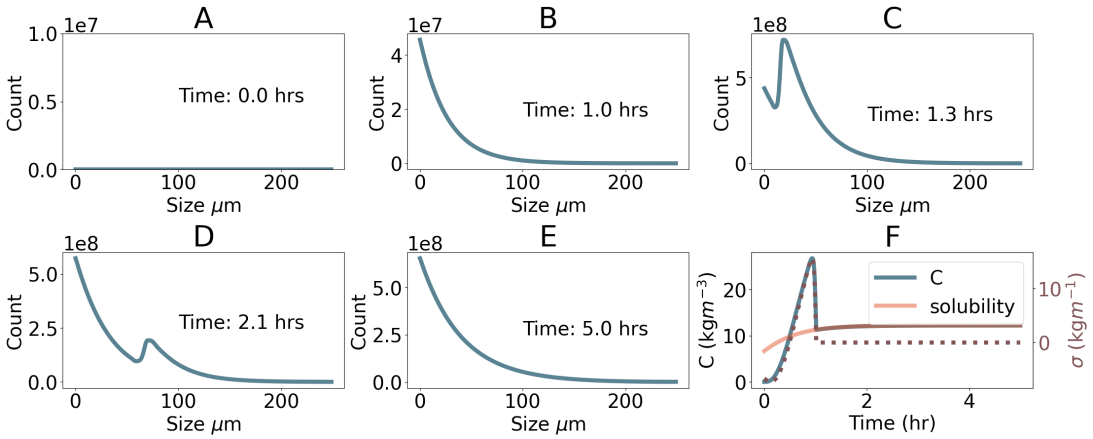

Figure 1: The crystal moments (zeroth through third), the unit's temperature, and the concentration/saturation levels throughout time (s) for the simulated reaction system: A + B → C↓ + D

Table 1: Parameters for the different runs.

	k_b $\left(\frac{\#}{\mathrm{m^3 s}}\right)$	E_b $\left(\frac{j}{mol}\right)$	b	k_s $\left(\frac{\#}{\mathrm{m^3 s}}\right)$	s	*s*2	k_g $\left(\frac{\mu m}{s}\right)$	E_g $\left(\frac{j}{mol}\right)$	g	k_r $\left(\frac{mol}{m^3 s}\right)$	E_r $\left(\frac{j}{mol}\right)$
1, 2A/2B	8.188	0	1.124	4.18 E+10	0.35	1	9.73	11280	0.2337	1 e-4	0
2C/2D	8.188	0	1.124	4.18 E+10	0.35	1	9.73	11280	0.2337	2e-4; 1.3e-4	0
2E/2F	8.188	0	1.124	4.18 E+10	0.35	1	9.73	11280	0.2337	2e-4; 1.3e-4	0

Figure 1 was generated using the simulator and demonstrates crystallization behavior consistent with a RC system. At t=0, there are no crystals in the RC. As the reaction progresses, the concentration exceeds the solubility, leading to a supersaturated solution as shown in Figure 1F. At a certain point (around 1 hour) nucleation occurs and the liquid concentration quickly reduces to and equilibrates at the solubility point. This results in a sudden uptick in counts of small crystals as seen in Figure 1B. The crystals from the large nucleation event then grow larger while more crystals are nucleating from the continuous addition of reactants. This results in a distribution with high counts of crystals near the nucleation length, and a higher count of crystals slightly larger than the nucleation length. This can be seen in Figure 1C. This batch of larger crystals continues to grow while more crystals nucleate and grow. At the same time, crystals leave the system through the outlet, lowering the count of older, larger crystals. Eventually, the larger crystals from the initial nucleation all leave and the steady state CSD is reached. This can be seen in Figure 1E.

Figure 2C-F showcases the advantage mentioned earlier of increased yield for reversible reactions or reactions where the target is an intermediary. Each column in the figure corresponds to a different reaction setup where species C is the target product, and each row corresponds to either a reactor with no crystallization or a RC. The liquid concentration shown decreases as species C crystallizes in the RC environments. The first reaction case (Figure 2A-B) is simple, and both the reactor and RC behave similarly as expected. If product D were the desired product, then using RC effectively removes the need for an additional separation step if the solubility of C is within the impurity tolerance allowed within D.

The second reactive case is reversible. Figure 2C-D shows that by crystallizing the product, the RC drives the reversible reaction forward due to Le Chatelier's principle. The black line is the overall accumulation of the target product. The figure depicts how the RC in a reversible reaction with these conditions results in a higher yield of the target product, generating 27.5 moles from the RC compared to 25.7 moles in the reactor. In the last reaction case (Figure 2E-F), the target species (C) is an intermediate product. The figure shows that the RC system successfully isolates species C before much of it can further react to form the undesired product E. This results once again in a higher yield of the target product than what a reactor could achieve in the same conditions, producing 25.8 moles from the RC compared to 21.2 moles in the reactor. The parameters used for each case can be found in Table 1. The crystallization parameters used were based on known parameters for paracetamol

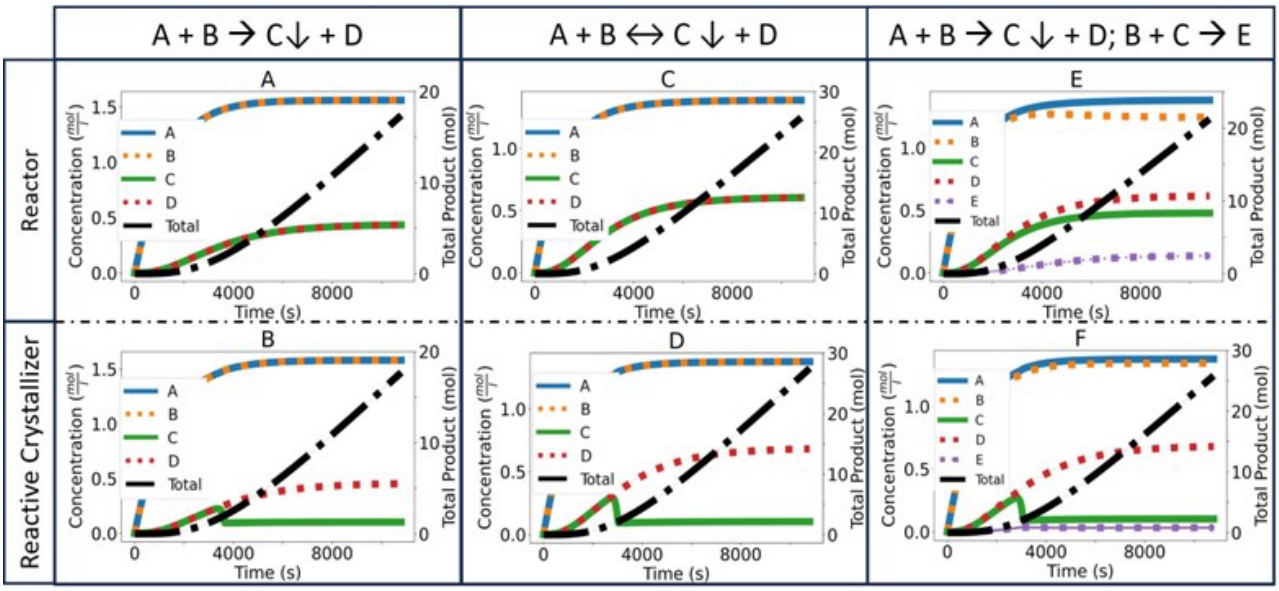

Figure 2: Figure comparing RC concentration profiles and non-crystallizing species profiles for different cases. Table 1 has the respective parameters of each case.

[10].

While these results are promising and demonstrate behavior consistent with RC, there are limitations to the model. In many RCs, the reaction is very fast with very quick precipitation and limited by mixing. This model assumes perfect mixing and therefore is less reliable with increasing effects of mixing non-idealities. If the solution can be considered homogeneous before nucleation occurs, then the model should accurately represent the system. Should the mixing become a significant limitation, a different model, such as one employing computational fluid dynamics balances, would be needed to account for the effects. This would introduce other limiting assumptions and is not the particular system of interest.

The cases discussed represent a non-exhaustive list of possible use cases of the model. They were chosen to showcase the potential advantages to RC and to establish that the model followed the expected behavior of a RC system. In each case explored, the reaction is exothermic; endothermic reaction effects have yet to be simulated. All of the cases discussed assumed the same crystallization kinetics, and so the full interaction between crystallization kinetics and reaction kinetics has yet to be determined.

Other reaction systems are conceivable, such as a reversible reaction with a competing byproduct, or a system where the byproduct influences solubility of the target species. Such cases were not simulated in this work for two reasons. First, cases A-F have results which are easily predicted, and so model behavior could be easily validated conceptually. The more complicated reaction systems would be harder to predict and validate conceptually, leading to less certainty of the model overall. Second, in the situation of the byproduct influencing the target species' solubility or other similar complications, cases A-F can be easily modified for the model to capture the behavior. The chosen cases were therefore considered reasonably representative of the systems of interest.

It should also be noted that, with certain parameter regimes, the model struggled to converge. While the exact relationship is still be investigated, increasing differences between the reaction rate and crystallization rate by magnitudes necessitated decreasing step sizes for the integrator to properly solve the equations. This consequently resulted in longer solve times. The parameters listed in Table 1 behave well together in the integrator. This could be caused by the fact that the chosen parameters closely resemble those of a real system whereas other parameter sets explored may not have had physical analogs resulting in difficulty converging. Further work is needed to truly define the reason for the convergence issues and determine how to avoid the issues.

CONCLUSION

In this work, a simulation model of a reactive crystallization (RC) was developed and demonstrated. The mathematical description of the system was provided, and the digital implementation was described. Three different case studies were used to show the behavior and yield of the RC system compared to that of a system using reactors and crystallizers in series. Irreversible reactions showed no differences in product yield whether using the RC or the reactor and crystallizer route was used. In other cases, which had reversible

reactions or a reaction system where the species of interest was an intermediary product, the RC improved yield. This behavior matched the predicted outcome and verified that the model predictions at least match the behavior expected of RC in various situations. Work is now being done to confirm the model predictions experimentally.

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