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Modeling and control of ibuprofen crystal growth and size distribution

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HIGHLIGHTS

- Multiscale modeling of ibuprofen batch crystallization.
- Calculation of evolution of ibuprofen crystal shape distribution.
- Model predictive control of ibuprofen crystal shape distribution.
- Comparison with standard control policies.

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ABSTRACT

In this work, we focus on multiscale modeling and control of a seeded batch crystallization process used to produce ibuprofen crystals. For the modeling of the crystal growth process, we consider kinetic Monte Carlo (kMC) simulations comprising of molecule adsorption, desorption, and migration type microscopic surface events. To account for growth rate variability, we propose a model for growth rate dispersion (GRD), based on the available experimental data, which will be applied at the individual crystal growth level in the kMC simulations. Finally, a model predictive controller (MPC) is developed in order to control the crystal size distribution of ibuprofen in the batch crystallization process and the MPC closed-loop performance is compared against constant temperature control (CTC) and constant supersaturation control (CSC) policies. The proposed MPC is able to deal with the constraints of the control problem, in addition to minimizing the spread of the crystal size distribution in a superior fashion compared to the other control methodologies, which improves the crystal product quality at the end of the batch.

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1. Introduction

Crystallization is a key separation process in the pharmaceutical industry which is estimated to be over a $1 trillion per year industry. It is used for drug purification, separation, and pre-formulation. A key consideration in crystallization is that in order to achieve desired crystal product quality, the process environment must be controlled appropriately. Otherwise, the target drug could lose purity, stability, and bio-availability.

Simulation techniques are valuable tools that can be used in crystal growth modeling which usually consist of equilibrium Monte Carlo (MC) and kinetic Monte Carlo (kMC) simulations, as well as molecular dynamics (MD) simulations (Lovette et al., 2008). A well-written book by Frenkel and Smit (2002), in addition to a review by Rohl (2003), goes into detail about the development of these simulation techniques. In regards to crystallization, MD simulations are quite helpful when looking at how molecules move and how they are incorporated into the crystal, however, the length and time scales of MD simulations make them difficult to use for process modeling (Lovette et al., 2008). On the other hand, kMC simulations allow for more realistic length and time scales by using rate equations that describe different microscopic phenomena. To this end, kMC simulation methods have been widely used to simulate molecular-level phenomena like crystal nucleation, growth, and aggregation (Bortz et al., 1975; Dai et al., 2005, 2008; Gillespie, 1976, 2007; Rathinam et al., 2003; Reese et al., 2001; Snyder et al., 2005; Gilmer and Bennema, 1972; Kwon et al. 2013a, b, 2014; Jolliffe and Gerogiorgis, 2015). Furthermore, kMC simulation methods have been successfully applied to compute the net crystal steady-state growth rate accounting for the dependence of the desorption and migration rates on the local surface micro-configuration. For that reason, we look to investigate the batch crystal growth process of ibuprofen, one of the most widely used

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non-steroidal anti-inflammatory drugs (NSAID), via kMC simulations in this work. Due to the lack of availability of primary nucleation rate data, we will consider a seeded batch crystallization process and keep the supersaturation at low enough levels that the impact of nucleation and crystal fines formation will be minimal compared to the amount of crystals seeded to the system.

Ibuprofen works by reducing prostaglandins, which are the hormones causing inflammation and pain in the body. These are usually referred to as local hormones since they only act close to the location where they are produced. Although they are helpful initially since swelling will restrict injured areas and increased blood flow will assist in healing, longer term pain is undesirable. Thus, many different types of painkillers are used, where ibuprofen is one of the most common and widely available choices. In the US, ibuprofen brand Advil was the top over the counter (OTC) brand by revenue in 2013 with just over $490 million.

More specifically, we first model the ibuprofen crystal growth process. In order to do this, we investigate the growth rates of the (001) and (011) faces via a kMC simulation model. To account for variability in experimental crystal growth rate data, we develop a model for growth rate dispersion (GRD) since this phenomenon is known to affect ibuprofen crystal growth rates and this model is applied at the individual crystal level. After that, a seeded batch crystallizer will be considered, requiring the development of mass and energy balances for the modeling of the continuous-phase variables and this macroscopic model is combined with the microscopic crystal growth model. Finally, the crystal size distribution will be controlled by a model predictive controller (MPC) and compared against classical control strategies used in industry.

2. Ibuprofen crystal growth

2.1. Kinetic Monte Carlo modeling and simulation

In the present work, we will use kinetic Monte Carlo (kMC) simulations in order to model the growth rates of ibuprofen crystal faces since crystal growth is a non-equilibrium process. Unlike equilibrium Monte Carlo simulations, kMC simulations add an element of time by using rate equations representing different microscopic phenomena. Furthermore, this allows modeling the dependency of the crystal growth rates on the surface micro-configuration, in addition to the ability to consider individual crystals, thereby allowing for a more realistic model for growth rate dispersion. Ibuprofen has unit cell parameters of $a = 14.397$ Å, $b = 7.818$ Å, $c = 10.506$ Å, and $\beta = 99.70^\circ$ with four molecules per unit cell (Shankland, 1996; Shankland and Wilson, 1997). For this work, we will consider an $N \times N$ lattice with one molecule per lattice site and periodic boundary conditions. The types of microscopic events we consider in our kMC simulations in order to model the crystal growth are adsorption, desorption and migration. Nearest neighbor lists will be used to aid the computational efficiency when calculating the total rates for each of the microscopic phenomena (Christofides et al., 2008). The rate equations considered in this work are set up similar to that of Durbin and Feher (1991) for lysozyme, however, they have been modified to account for available growth rate data of ibuprofen on the (001) and (011) faces (Nguyen et al., 2014). Cano et al. (2001) reported data for all three faces (i.e., (001), (011), and (100)), however, they conducted their experiments at very low supersaturation ($\sigma = 0.013$) which is much lower than the supersaturation range of our study ($0.68 \le \sigma \le 1.20$), and thus, we were not able to use their data for comparison purposes in the present study. If more data becomes available in the future for the (100) face, then the dynamics of the (100) face can easily be integrated into the present kMC simulation model.

2.2. Rate equations

The per-site adsorption rate is defined as

$$r_a = K_a \sigma, \tag{1}$$

where K_a is the adsorption coefficient and σ is the relative supersaturation of the system defined by the following equation:

$$\sigma = \frac{\frac{I}{E} - \frac{I^*}{E}}{\frac{I^*}{E}}, \tag{2}$$

where I is the ibuprofen content, E is the ethanol content, and I^*/E is the solubility. The solubility will be taken from Rashid et al. (2008, 2011) and is defined as

$$\frac{I^*}{E} = 0.497 + 0.001026 T^2, \tag{3}$$

with temperature T defined in degrees Celsius. Since we consider an $N \times N$ lattice model, the total rate of adsorption is simply

$$W_a = N^2 r_a. \tag{4}$$

Unlike adsorption, the rates of desorption and migration will be dependent on the local environment at each lattice site (i.e., number of nearest neighbors to this site). When a particle has a high number of nearest neighbors, a lower desorption/migration rate will be associated with this site due to the fact that the particle is more stable in its current location. Likewise, when a particle has very few or no nearest neighbors, that particle will have a higher desorption/migration rate. Thus, we will use an Arrhenius type equation for the per-site rate of desorption, r_d, which is defined as follows:

$$r_d(i) = K_d \exp\left(-i \frac{E_{pb}}{k_B T}\right), \tag{5}$$

where K_d is the desorption coefficient, i is the number of nearest neighbors for the current lattice site ranging from zero to four (N, S, E, W directions), E_{pb} is the binding energy per bond, k_B is the Boltzmann constant, and T is the temperature in Kelvin. In order to find the total rate of desorption, we sum over the entire lattice. This can be done in a simple way by taking advantage of the fact that there are five different types of local environments, rather than checking each individual lattice site requiring an $O(N^2)$ calculation. Thus, the total rate of desorption is

$$W_d = \sum_{i=0}^{4} W_{d_i}, \quad W_{d_i} = M_i r_d(i), \tag{6}$$

where W_{d_i} is the total rate of desorption for lattice sites with i nearest neighbors and M_i is the number of lattice sites with i nearest neighbors. Migration works in an analogous way and is defined as follows:

$$r_m(i) = K_m \exp\left(-i \frac{E_{pb}}{k_B T}\right), \tag{7}$$

$$W_m = \sum_{i=0}^{4} W_{m_i}, \quad W_{m_i} = M_i r_m(i), \tag{8}$$

where r_m is the per-site rate of migration, K_m is the migration coefficient, W_m is the total rate of migration, and W_{m_i} is the total rate of migration for lattice sites with i nearest neighbors. Lastly, the amount of time elapsed when an event occurs is defined in the following way:

$$\Delta t = -\ln(1-\zeta)/W_{\text{tot}}, \tag{9}$$

where ζ is a uniform random number, i.e., $\zeta = [0, 1)$, and $W_{\text{tot}} = W_a + W_d + W_m$.

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