Anti-Fouling Control of Plug-Flow Crystallization via Heating and Cooling Cycle

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Abstract: Plug-flow crystallization (PFC) is a promising continuous pharmaceutical crystallization process but is prone to fouling due to uncontrolled crystallization on the reactor surface (encrustation). This results in operational issues such as (1) flow blockage, (2) increased thermal resistance, and (3) reduced supersaturation, and in turn leads to limited continuous operation and reduced crystal quality and yield. In this work, we introduce a model-based anti-fouling control (AFC) via spatial and temporal heating and cooling cycle.

Keywords: Spatio-Temporal Control, Process Control, Model-Based Control, Dynamic Modeling, Dynamic Optimization, Continuous Crystallization, Plug Flow, Fouling.

1. INTRODUCTION

Crystallization is an essential unit operation in the pharmaceutical industry and has recently received increased attention due to its potential for continuous operation [Nagy and Braatz (2012); Alvarez and Myerson (2010)]. When compared to batch crystallization, its continuous counterpart has a potential for significant process improvements in terms of robustness, productivity and product quality. Plug flow crystallizer (PFC) is a promising candidate for continuous crystallization system due to its fast startup dynamics and flexible temperature and (anti-)solvent control when compared with other types of continuous reactor, such as mixed-product mixed-suspension reactor (MSPR)[Lawton et al. (2009)]. In addition, more advanced control of crystal quality using PFC has recently been demonstrated, including in dissolution of crystal fines [Majumder and Nagy (2013)] and multi-objective control of crystal quality in terms of coefficient of variation (CV) and crystal mean size (L_{43}) [Ridder et al. (2014)]. Nevertheless, PFC is associated with a common operational issue which prevents it from being the ideal continuous crystallizer, namely *encrustation* [Majumder and Nagy (2014); Bohnet (1987); Brahim et al. (2003). Encrustation is a phenomena by which uncontrolled crystallization takes place at the reactor surface, resulting in a number of operational issues, such as (1) flow blockage, (2) reduced heat transfer (due to increased thermal resistance), and (3) reduced supersaturation. These events in turn lead to limited continuous operation and reduced crystal quality and yield. In this work, we introduce a model-based anti-fouling control (AFC) via spatial and temporal heating and cooling cycle, whereby continuous crystallization operating conditions in terms of temperature profile across different segments of the PFC is determined such that encrust is periodically dissolved with minimal impact on product quality and yield. The paper is organized as follows: Section 2 describes

the dynamic model of encrustation coupled with the crystallization dynamics in a PFC. Two case studies were subsequently performed in Section 3 in which the effects of encrustation on a PFC were simulated when (i) crystal growth is maximized and (ii) encrustation is minimized. Section 4 discusses the model-based AFC design concluded with plans for future work and design improvements.

2. POPULATION BALANCE MODELING WITH ENCRUSTATION DYNAMICS

The PFC-PBM dynamics is given by:

$$\frac{\partial}{\partial t}(A_f n) + \frac{\partial}{\partial z}(u_z A_f n) + \frac{\partial}{\partial L}(GA_f n) = 0,$$
B.C.: $G(S)n(t, L, z)|_{L=0} = B(S),$
 $n(t, L, z)|_{z=0} = n_{seed}(L),$ (1)

where n is the crystal size distribution (CSD), u_z is the slurry flow velocity, G is the crystal growth rate, B is the nucleation rate, and n_{seed} is the seed CSD, z is the reactor axis, and L is the crystal size axis. Here, $A_f(t, z) = \pi R_f^2(t, z)$ is the flow area within the tube which changes with time and along the reactor length due to encrustation.



Fig. 1. Graphical representation of encrustation-PBM-PFC dynamical model with different domains.

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Majumder and Nagy have developed a model for encrustation in a PFC inspired from fouling kinetics commonly found in heat exchangers (Fig. 1). The encrustation dynanmics can be summarized as follows:

$$\begin{aligned} \frac{d\delta}{dt} &= k_E \frac{d\chi}{dt} = \frac{k_m}{\rho_E} \frac{dm}{dt} \\ &= \frac{k_m}{\rho_E} \left[\frac{1}{2} \frac{k_m}{k_R} + (C_b - C_{\text{sat}}) \\ &- \left(\frac{1}{4} \frac{k_m^2}{k_R^2} + \frac{k_m}{k_R} (C_b - C_{\text{sat}}) \right)^{1/2} \right] \\ &- \frac{\rho_E}{83.2w^{0.54}} \left(1 + \alpha \Delta T \right) d_p \left(\rho_L^2 \eta g \right)^{1/3} w^2 \delta, \end{aligned}$$

where,

$$k_R = k_{R0} \exp\left(-\frac{\Delta E_f}{RT_f}\right),$$

$$T_f = T + 0.55 \left(T_R|_{r=R_f} - T\right).$$
(2)

Here, δ is the encrust thickness, k_E is the thermal conductivity, χ is the thermal resistance, ρ_E is the encrust density, m is the encrust mass, k_m is the mass transfer coefficient of solute from the bulk solution to the encrust film, k_R is the Arrhenius-type adsorption rate of solute to encrust, C_b is the bulk solute concentration, C_{sat} is the saturation concentration within the film layer, w is the bulk fluid velocity. α is the linear expansion coefficient, ΔT is the temperature difference between the reactor wall and the encrust surface, d_p is the encrust particle diameter, η is the film viscosity, and g is the gravitational acceleration. In addition, the mass transfer coefficient can be semiempirically calculated using the Sherwood number:

$$Sh = 0.034 \text{Re}^{0.675} \text{Sc}^{1/3},$$
$$Sh = \frac{2R_f k_m}{D}, \text{ Re} = \frac{2R_f w \rho_L}{\eta}, \text{ Sc} = \frac{\eta}{\rho_L D}.$$
(3)

Here, R_f is the PFC radius, D is the solute diffusivity, ρ_L is the bulk liquid density, Re is the Reynold's number, and Sc is the Schmidt number. The encrustation kinetics is coupled with the PFC-PBM dynamics as well as the energy and mass balances. The energy balance is divided into three regions (Fig. 1), namely conduction across the reactor wall ($\Omega_W : r \in [R_f, R_0]$), conduction across the encrust ($\Omega_E : r \in [R_i, R_f]$) and the convection within the tube ($\Omega_T : r \in [0, Ri]$). Both the conduction and convection dynamics yield the following set of coupled differential equations:

$$\begin{aligned} \text{Wall} &: \frac{\rho_W C_{p,W}}{k_W} \frac{\partial T_W}{\partial t} = \frac{1}{r} \frac{\partial T_W}{\partial r} + \frac{\partial^2 T_W}{\partial r^2} + \frac{\partial^2 T_W}{\partial z^2}, \\ \text{Encrust} &: \frac{\partial T_E}{\partial t} = \frac{k_E}{\rho_E C_{p,E}} \left[\frac{1}{R_i - \tilde{r}\delta} \left(\frac{-1}{\delta} \right) \frac{\partial T_E}{\partial \tilde{r}} \right. \\ &+ \frac{1}{\delta^2} \frac{\partial^2 T_E}{\partial \tilde{r}^2} + \frac{\partial^2 T_E}{\partial z^2} \right], \\ \text{Tube} &: \frac{\partial}{\partial t} (A_f T) = -\frac{\partial}{\partial z} (uA_f T) + \frac{k}{\rho C_{p,L}} + \\ &\quad \frac{\partial}{\partial z} \left(A_f \frac{\partial T}{\partial z} \right) + \frac{2\pi R_f h}{\rho C_{p,L}} (T_E|_{R_f} - T), \end{aligned}$$

where $\tilde{r} = \frac{R_i - r}{\delta}$ is a dimensionless radial coordinate defined such that its range stays between 0 $(r = R_i)$

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and 1 $(r = R_f)$ irrespective of the encrust thickness. The boundary conditions are given as:

B.C.:
$$-k_W \frac{\partial T_W}{\partial r}\Big|_{r=R_i} = -k_E \frac{\partial T_W}{\partial r}\Big|_{\tilde{r}=0},$$

 $: T_W|_{r=R_i} = T_E|_{\tilde{r}=0},$
 $: -k_E \left(-\frac{1}{\delta}\right) \frac{\partial T_E}{\partial \tilde{r}}\Big|_{\tilde{r}=1} = -h \left(T_E|_{r=R_f} - T\right),$
 $: T|_{z=0} = T_{in},$
(5)

where axial symmetry is assumed, h is the overall heat transfer coefficient and $C_{p,L}$ is the specific heat capacity of the liquid slurry. The mass balance in turn is given as:

$$\frac{\partial}{\partial t}(A_f C) = -\frac{\partial}{\partial z}(u_z A_f C) - \frac{\rho_c}{\rho_L}\phi_\nu \frac{\partial}{\partial t}(A_f \mu_3)
2\pi \frac{\rho_E}{\rho_L}(R_i - \delta)\frac{\partial\delta}{\partial t},
\rho_E = (1 - \epsilon)\rho_c + \epsilon\rho_L,$$
(6)

where $\mu_3 = \int_0^\infty L^3 n(t, L, z) \, dL$ is the third moment of the CSD and α_{ν} is the volumetric shape factor. ρ_E is the encrust density and is inferred from the encrust void fraction ϵ . PBM is a non-linear PDE known to have very sharp dynamics and discontinuities. A high-resolution finite volume method (HRFV)[Gunawan et al. (2004)] has proved to be a robust numerical method for solving the PBM equation and is thus applied on (1). First, a 'cell' averaging of the CSD is defined:

$$n_{i,j} = \frac{1}{\Delta L \Delta z} \int_{L_{i-1/2}}^{L_{i+1/2}} \int_{z_{j-1/2}}^{z_{j+1/2}} n(t, L, z) dL \, dz.$$
(7)

When (7) is substituted into (1), this yields a set of finite difference ODEs:

$$\frac{d}{dt}(A_f n)_{i,j} = \frac{1}{\Delta L} \left(G A_f n|_{i+1/2,j} - G A_f n|_{i-1/2,j} \right) - \frac{1}{\Delta z} \left(u_z A_f n|_{i,j+1/2} - u_z A_f n|_{i,j-1/2} \right). \quad (8)$$

Note that A_f only varies in the z direction and is therefore only associated with the index j and is constant along i. The HRFV method uses Van Leer's Flux Limiter to ensure that the fluxes between the cell boundaries are sufficiently smooth. The flux is the weighted average of two cells given by:

$$n_{i+1/2,j} = n_{i,j} + \phi(r_{i+1/2,j})(n_{i+1,j} - n_{i,j}), \qquad (9)$$

where $\phi(r)$ is the Van Leer's Flux Limiter defined as:

$$r_{i+1/2,j} = \frac{n_{i,j} - n_{i-1,j} + e}{n_{i+1,j} - n_{i,j} + e},$$

$$\phi(r_{i+1/2,j}) = \frac{r_{i+1/2,j} + |r_{i+1/2,j}|}{1 + |r_{i+1/2,j}|}.$$
(10)

Here, e is a small value to prevent division by 0. Analogous expressions can be defined in terms of the index j+1/2 for $n_{i,j+1/2}$, $r_{i,j+1/2}$ and $\phi(r_{i,j+1/2})$. The B.C.'s in (1) applies to the fluxes at the boundary as follows:



Fig. 2. Optimization of crystal mean size in the presence encrustation. (Top left) Crystal size distribution (CSD), (Top right) temperature profile, (Bottom left) supersaturation, (Bottom right) encrustation. Both the CSD and temperature profile were taken at the 12-th RT. The figure shows how the dynamics is initially dominated with encrust formation followed by crystal formation.

for
$$i = 0$$
: $n_{i+1/2,j} = \frac{B(S_j)}{G(S_j)}$,
 $i = 1$: $n_{i+1/2,j} = \frac{n_{i,j} + n_{i+1,j}}{2}$,
 $i = N_L$: $n_{i+1/2,j} = n_{N_L,j}$,
 $j = 0$: $n_{i,j+1/2} = n_{seed}$,
 $j = 1$: $n_{i,j+1/2} = \frac{n_{i,j} + n_{i,j+1}}{2}$,
 $j = N_z$: $n_{i,j+1/2} = n_{i,N_z}$. (11)

Here, $N_L(20)$ and $N_z(20)$ corresponds to the grid size in the direction of crystal size and reactor length, respectively. In the case of undersaturation, the PBM equation becomes:

$$\frac{\partial}{\partial t}(A_f n) + \frac{\partial}{\partial z}(u_z A_f n) - \frac{\partial}{\partial L}(DA_f n) = 0,$$

B.C.: $n(t, L, z)|_{L=0} = 0,$ (12)

where D is the dissolution rate. The HRFV flux expressions and the B.C's for the cell in which dissolution take place may in turn be appropriately modified with respect to the crystal size index i (The B.C's in terms of j stays

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the same).

$$n_{i+1/2,j} = n_{i,j} + \phi(r_{i+1/2,j})(n_{i,j} - n_{i+1,j}),$$

for $i = 0$: $n_{i+1/2,j} = n_{1,j},$
 $i = N_L - 1$: $n_{i+1/2,j} = \frac{n_{N_L - 1,j} + n_{N_L,j}}{2},$
 $i = N_L$: $n_{i+1/2,j} = 0.$ (13)

These dynamical models are subsequently used to simulate a number of optimization case studies as well as study a particular design of AFC.

3. CASE STUDIES

3.1 Optimization of crystal mean size in the presence of fouling

The purpose of this simulation study is to compare the optimal crystallization dynamics for maximizing crystal mean size with and without fouling. The crystal mean size criteria used is the L_{43} , i.e. the ratio of the fourth and



Fig. 3. Comparison between PFC with and without fouling. (Top) Residence time (RT) and % blockage when fouling is not present the line stays flat from the beginning (data not shown), (Middle) CSD, (Bottom) Supersaturation.

third moment of the CSD. The optimization problem is formulated as:

$$\max_{T_i} \mathcal{J}(\mathcal{T}) = L_{43}(\mathcal{T}),$$

$$i \in [1, 4], \ \mathcal{T} = 12\tau, \ \tau = \frac{u_z}{Z}$$
s.t.:
$$(1) \text{ to } (6),$$

$$20 \leq T_i \leq 40,$$
for S > 0:
$$G(S, L) = k_G \exp\left(-\frac{\Delta E_G}{RT}\right) (1 - \exp\left(-\gamma\left(L+\beta\right)\right)) (\sigma - 1)$$

$$B(S) = J_{\text{prim}} + J_{\text{sec}},$$

$$J_{\text{prim}} = j_a \exp\left(\frac{j_b}{T^3(\ln \sigma)^2}\right),$$

$$J_{\text{sec}} = k_b M_T^2 S^b,$$

$$M_T = \rho_c \alpha_\nu \mu_3,$$

$$\sigma = \frac{C}{C_{\text{sat}}},$$

$$S = C - C_{\text{sat}},$$

$$C_{sat} = AT + BT^2 + CT^3$$
for S < 0:
$$D(S, L) = \frac{k_D}{L_g} (-S)^d.$$
(14)



Fig. 4. Comparison between Case Study 3.1 and 3.2. (Top) Encrust thickness and (Bottom) Crystal mean size (L_{43}) . The figure shows that fouling can be significantly reduced should the crystal growth requirement be sufficiently low (10 % vs. 40 % blockage).

Note that the reactor is divided into 4 equal halves, each associated with its own wall temperature. Additionally, the seed is modeled as a normally distributed crystal size density as follows:

$$n_{\text{seed}} = \frac{\kappa}{\sigma_{\text{seed}}\sqrt{2\pi}} \exp\left(-\frac{\left(L - \mu_{\text{seed}}\right)^2}{\sigma_{\text{seed}}^2}\right), \quad (15)$$

where κ is a scaling factor which is determined according to the desired the seed mass fraction. The full list of all parameter values is given in Table A.1. Genetic algorithm (GA) is used as the optimization routine of choice, with the initial conditions (I.C's) set according to the following $_{g}$ settings: (1) the tube temperature equals the in-flow temperature at 38 o C, (2) the tube concentration starts at supersaturation, and (3) there is no initial crystal or encrust. As seen in the Fig. 3, while the optimization leads to formation of large crystals, it also results in significant encrust formation, rendering it a batch process after 12 residence time (RT). In addition, when the result is compared with crystallization without fouling, not only is blockage prevented, but the heat transfer dynamics and supersaturation level is reduced such that both the crystal mean size and yield is higher (Fig. 4).

3.2 Minimization of encrustation with minimal crystal growth

In this study, an optimization is performed to see if the rate of encrustation could be reduced while maintaining crystal growth. The problem formulation is expressed analogously to the first case as follows:

$$\min_{T_i} \mathcal{J}(\mathcal{T}) = |\delta(\mathcal{T})|_{\infty},$$

 $i \in [1, 4], \ \mathcal{T} = 12\tau, \ \tau = \frac{Z}{u_z}$
s.t.:
(1) to (6), (14) and (15) (16)

The same simulation parameters, including B.C's and I.C.'s, and optimization routine is used. The results is shown in Fig. 4 and it demonstrates how the extent of encrust formation may be significantly decreased at the expense of moderate crystal mean size reduction such that the PFC operation can be prolonged. While the two case studies illustrates the two extremes of the trade-offs between crystal quality and continuous operation, in the next section, we describe an implementation of antifouling control (AFC), which can eliminate fouling without sacrificing crystal quality.

4. MODEL-BASED ANTI-FOULING CONTROL (AFC)

The AFC design divides the multi-segment PFC into two symmetric parts, which periodically cycle between cooling and heating regions. Here, the design objective is two-fold: (i) in the cooling segment, the temperature is optimized such that crystal growth is maximized, while (ii) complete dissolution is enforced and at the same time the effect on crystal dissolution is minimized in the heating segment. The optimization problem can be formulated as follows:

s.t. :

$$\max_{T_i} \mathcal{J}(\mathcal{T}) = L_{43}(\mathcal{T})$$

(1) to (6), (14) and (15), and
in cooling segment :20
$$\leq T_i \leq 35$$
,
in heating segment :39 $\leq T_i \leq 45$. (17)

The upper and lower bounds of the different temperature segments are chosen to ensure that only growth and dissolution takes place in the designated cooling and heating regions, respectively. In addition, the optimization is periodically performed at the end each optimization horizon with a new set of I.C's obtained from the previous run. In the first cycle, the I.C's are the same as Case study 1 and 2 except that there is an initial encrust thickness. It is important to note that since the temperature profile within the tube cannot be manipulated arbitrarily such that supersaturation is maintained while encrust is dissolving, undersaturation must always take place in the leading part of the dissolution segment causing the crystal to decrease in size (Fig. 5, 1st row). Specifically, there are two reasons why the temperature control within the tube is limited; the first is that the jacket temperature is constant over the length of the segment and the second is because there is a natural heat transfer dynamics which dictates the rate of heat conducted from the wall through the encrust and into the tube. Consequently, optimal spatial and temporal cooling and heating temperature profile must be obtained such that overall crystal growth takes place along the



Fig. 5. Simulation of AFC via spatial and temporal heating and cooling cycle in the 1st (left) and 2nd cycle (right). The top row corresponds to the dynamics of the CSD while the second row refers to that of the encrust.



Fig. 6. AFC with recycling according to desired L_{43} setpoint.

reactor, all the while encrust formation and dissolution are periodically cycled between the segments so as to maintain continuous operations (Fig. 5, 2nd row). Furthermore, in the case where dissolution of the crystal during the heating region has a significant impact on the L_{43} , a lower bound on the process output can be used to determine the time point of product recycling (Fig. 6).

5. CONCLUSION

In this paper, a model-based approach for AFC design for a continuous crystallization using a PFC is introduced and compared with two case studies where crystal growth is maximized and encrust thickness is minimized. The control design demonstrates a proof-of-concept for a completely continuous PFC operation in which encrust is periodically negated and without reduction in crystal mean size if an additional recycling process is implemented. Future work should involve experimental verification of simulated work and further studies on the effect of product recycling.

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Appendix A. SIMULATION PARAMETER VALUES

Table A.1. PFC-PBM parameters.

Parameter	Value	Units
$ ho_W$	2230	$kg.m^{-3}$
$C_{P,W}$	753	$J.Kg^{-1}K^{-1}$
k_W	1.005	$W.m^{-1}K^{-1}$
$ ho_E$	1750	$kg.m^{-3}$
$C_{P,E}$	870	$J.Kg^{-1}K^{-1}$
k_d	1.27×10^{-2}	$\mathrm{m.s}^{-1}$
k_E	1.11	$W.m^{-1}K^{-1}$
k_{R0}	2.36×10^{6}	$\mathrm{m}^{4}\mathrm{Kg}^{-1}\mathrm{s}^{-1}$
d_p	36×10^{-6}	m
D	1.57×10^{-9}	$\mathrm{m}^{2}\mathrm{s}^{-1}$
E	37143	$J.mol^{-1}$
α	1×10^{-6}	K^{-1}
η	600×10^{-6}	Pa.s
ϵ	0.2	-
ρ_l	1080	kg.m ⁻³
$C_{P,l}$	4185.5	$J.Kg^{-1}K^{-1}$
k	0.58	$W.m^{-1}K^{-1}$
h	1000	$W.m^{-2}K^{-1}$
ja	1.70×10^{8}	$\#m^{-3}s^{-1}$
Ĵь	5.64×10^{6}	K^3
k_b	3.14×10^{7}	$m^{-3}s^{-1}$
j	1	-
\tilde{b}	1.32	-
K_{G0}	2.05×10^{5}	$\rm m.s^{-1}$
g	1.42	-
γ	7.18×10^{2}	-
β	6.10×10^{5}	m
ΔE_G	5.77×10^{4}	$J.mol^{-1}$
ϕ_v	0.62	-
k_D	10.72×10^{-9}	$\mathrm{m.s^{-1}}$
\overline{q}	0.51	-
\hat{d}	0.34	-
A	4.58×10^{-5}	-
B	2.43×10^{-4}	-
C	4.63×10^{-2}	-
Z	2.40	m
R_{f}	7.5	mm
R_0	9.5	mm
Q	40	$mL.min^{-1}$
κ	1×10^{8}	-
μ _{scod}	54	μ m
$\sigma_{\rm rec}$	15	μm
seea	10	P****