18th European Symposium on Computer Aided Process Engineering – ESCAPE 18
Bertrand Braunschweig and Xavier Joulia (Editors)

A population balance model approach for crystallization product engineering via distribution shaping control

Zoltan K. Nagy

Chemical Engineering Department. Loughborough University, Loughborough, LE11 3TU, United Kingdom

Abstract

The paper presents a practical control approach, which can be used to directly design the shape of a crystal size distribution, to robustly achieve desired product properties. The control approach is implemented in a hierarchical structure where on the lower level a model-free crystallization control methodology, the supersaturation control, drives the system in the phase diagram, rather than in the time domain, whereas on the higher level a robust on-line model based optimization algorithm adapts the setpoint of the supersaturation controller to counteract the effects of changing operating conditions. The process is modeled using the population balance equation, which is solved using an efficient implementation of the method of characteristics.

Keywords: distribution shaping control, population balance modeling, method of characteristics, optimal control, quadrature method of moments.

1. Introduction

Crystallization is one of the key unit operations in pharmaceutical, food and fine chemicals industries. Despite the long history and widespread application of batch crystallization, there remains a disproportionate number of problems associated with its control [1], mainly related the complex nonlinear dynamics with non-ideal mixing, and various disturbances characteristic to these systems. The operating conditions of the crystallization process determine the physical properties of the products which are directly related to the crystal size distribution (CSD), shape or polymorphic form. These properties determine the efficiency of downstream operations, such as filtration, drying, and tablet formation, and the product effectiveness, such as bioavailability and shelf-life. With the recent change of industrial procedures from Quality-by-Testing (QbT) to Quality-by-Design (QbD) and the advent of process analytical technology (PAT) initiative, especially in the pharmaceutical industries, approaches which can be used to design desired product properties are of great interest. The classical control objectives expressed in characteristics of the size distribution (e.g. maximize average size, minimize coefficient of variation) can lead to conservative and economically inefficient designs of the crystallization systems [2]. The paper presents an approach which can be used to directly design the shape of a crystal size distribution, to achieve desired product properties. Since dissolution rate depends on the shape of the CSD, when the resulting crystals represent the final product (e.g. drugs for inhalers) controlling the shape of the CSD can provide novel applications in the area of drug delivery, or environmentally friendly dosage of pesticides, where particular multimodal distributions can be designed to achieve desired concentration level of the active compound. The crystallization system is modeled via a population balance equation which is directly used in the

optimization procedure where the objective function is expressed in terms of the shape of the entire CSD. The population balance model (PBM) is solved using an efficient implementation of the method of characteristics [3] when nucleation and growth are the governing mechanisms, and with the quadrature method of moments (QMOM) when agglomeration and breakage are also considered [4]. It is shown that in special cases when constant supersaturation control is applied analytical solution of the PBM is possible for the case of generic power law growth kinetics. The optimization problem is solved using an efficient multistage approach implemented in the optimization package OptCon. The proposed approach is corroborated in the case of a simulated crystallization system.

2. Population balance modelling of the batch crystallization process

2.1. PBM with growth and nucleation kinetics only

Considering a single growth direction with one characteristic length L, and a well-mixed crystallizer with growth and nucleation as the only dominating phenomena the population balance equation (PBE) has the form

$$\frac{\partial f_n(L,t)}{\partial t} + \frac{\partial\{G(S,L;\theta_g)f_n(L,t)\}}{\partial L} = B(S;\theta_b)\delta(L_0,L)\,, \tag{1}$$

where $f_n(L,t)$ is the crystal size distribution expressed in the number density function (number of crystal per unit mass of slurry), t is time, $G(S,L;\theta_g)$ is the rate of crystal growth, $B(S;\theta_b)$ is the nucleation rate, S = (C-C_{sat}) is the supersaturation, C is the solute concentration, C_{sat} = C_{sat}(T) is the saturation concentration, and θ_g and θ_b are vectors of growth and nucleation kinetic parameters, respectively. Equation (1) can be transformed into a homogeneous hyperbolic equation with boundary condition $f(L_0,t) = B(S)/G(S)$ and initial condition given by the size distribution of seed, $f(L,0) = f_{seed}(L_0)$. The partial differential equation can be reduced to a system of ODEs by applying a combination of the method of characteristics (MoC) and method of moments (MoM). The aim of the MoC is to solve the PDE by finding characteristic curves in the $L-t$ plane that reduce the PDE to a system of ODEs. The $L-t$ plane is expressed in a parametric form by $L = L(\mathcal{Z})$ and $t = t(\mathcal{Z})$, where the parameter $\mathcal{Z}$ gives the measure of the distance along the characteristic curve. Therefore $f_n(L,t) = f_n(L(\mathcal{Z}),t(\mathcal{Z}))$, and applying the chain rule gives:

$$\frac{df_n}{d\mathcal{Z}} = \frac{dL}{d\mathcal{Z}}\frac{\partial f_n}{\partial L} + \frac{dt}{d\mathcal{Z}}\frac{\partial f_n}{\partial t}\,. \tag{2}$$

Considering size independent growth and comparing (2) with (1) we find $\mathcal{Z} = t$ and the characteristic curve is given by

$$\frac{dL}{dt} = G\,. \tag{3}$$

Adding (3) to the equations which results by applying the MoM, we can calculate the characteristic curve and boundary conditions $f(L_0,t)$ by the following ODEs,

$$\begin{aligned}\frac{d\mu_0}{dt} &= B \\ \frac{d\mu_j}{dt} &= G\mu_{j-1} + BL_0^j, \quad j = 1,2,3\,, \\ \frac{dL}{dt} &= G\end{aligned} \tag{4}$$

with initial conditions $x_0 = [\mu_0(0), \mu_1(0), \mu_2(0), \mu_3(0), 0]$ where the *j*th moment μ_j is defined by

$$\mu_j = \int_0^\infty L^j f_n(L,t)dL, \quad j = 0,\ldots,\infty\,. \tag{5}$$

The solute concentration is given by

$$C(t) = C(0) - k_v\rho_c(\mu_3(t) - \mu_3(0))\,, \tag{6}$$

where ρ_c is the density of crystals and k_v the volumetric shape factor.

2.2. PBM with breakage and agglomeration kinetics

The dynamic population balance equation for a closed homogenous system considering a single characteristic size is written,

$$\begin{aligned}\frac{\partial f_n(L)}{\partial t} = &\underbrace{\int_L^\infty b(L,\lambda)\,a(\lambda)\,f_n(\lambda)\,\mathrm{d}\lambda}_{\text{birth due to breakage}} + \underbrace{\frac{L^2}{2}\int_0^L \frac{\beta\left(\left(L^3-\lambda^3\right)^{1/3},\lambda\right) f_n\left(\left(L^3+\lambda^3\right)^{1/3}\right) f_n(\lambda)}{\left(L^3-\lambda^3\right)^{2/3}}\mathrm{d}\lambda}_{\text{birth due to agglomeration}} \\ &- \underbrace{a(L)\,f_n(L)}_{\text{death due to breakage}} - \underbrace{f_n(L)\int_0^\infty \beta(L,\lambda)\,f_n(\lambda)\,\mathrm{d}\lambda}_{\text{death due to agglomeration}} + \underbrace{\frac{\partial\left(G(L)\,f_n(L)\right)}{\partial L}}_{\text{growth}} + \underbrace{\delta(0,L)\,B_0}_{\text{nucleation}}\end{aligned} \tag{7}$$

where *β, a, G, B* and *b* are the aggregation kernel, breakage kernel, growth rate, nucleation rate and the daughter particle size distribution, respectively. The quadrature method of moment (QMOM) is based on the transformation

$$\mu_k = \int_0^{+\infty} f_n(L)\,L^k\,\mathrm{d}L \approx \sum_{i=1}^N w_i L_i^k \tag{8}$$

After moment transformation and applying the quadrature rule the model is given by

$$\begin{aligned}\frac{\mathrm{d}\mu_k}{\mathrm{d}t} = &\underbrace{\sum_{i=1}^N w_i a(L_i) b(k,L_i)}_{\text{birth due to breakage}} + \underbrace{\frac{1}{2}\sum_{i=1}^N w_i \sum_{j=1}^N w_j \left(L_i^3 + L_j^3\right)^{k/3} \beta\left(L_i,L_j\right)}_{\text{birth due to agglomeration}} - \underbrace{\sum_{i=1}^N w_i a(L_i) L_i^k}_{\text{death due to breakage}} \\ &- \underbrace{\sum_{i=1}^N w_i L_i^k \sum_{j=1}^N w_j \beta\left(L_i,L_j\right)}_{\text{death due to agglomeration}} + \underbrace{k\sum_{i=1}^N w_i L_i^{k-1} G(L_i)}_{\text{growth}} + \underbrace{\delta(0,k)\,B}_{\text{nucleation}}\end{aligned} \tag{9}$$

The breakage and agglomeration kernels depend on mixing conditions. Optimizing the power input to the system which determines the turbulent kinetic energy it is possible to minimize breakage or agglomeration.

3. Application of the batch NMPC for crystallization product design

For the case studies crystallization of paracetamol in water was considered as the model system, for which both the 1D and 2D growth kinetics were determined, by performing D-optimal experimental design. Samples were taken every 10 minutes and the characteristic sizes were determined by using image analysis. Different product design problems were considered, when various objective functions expressed as function of the CSD ($f(CSD;\theta)$) were optimized, by determining the required temperature profile, seed characteristics (distribution and mass) as well as mixing characteristics (overall turbulent kinetic energy), which can be expressed by the generic robust formulation

$$\min_{\substack{T(t)\\Seed\\Mixing}} \{(1-w)\mathcal{E}[f(CSD;\theta)] + wV[f(CSD;\theta]\} \tag{10}$$

where $\mathcal{E}(\cdot)$ and $V(\cdot)$ are the mean and variance of the performance index, respectively corresponding to the uncertain model parameter vector θ. Equation (10) generally is subject to various operational, productivity and quality constraints.

In the first case study the optimization problem is expressed as follows

$$\min_{T(t),m_{seed},\bar{L}_{seed},\sigma_{seed}} \{(1-w)\sum_k (f_n(L_k,t_f;\hat{\theta}) - f_n^{desired}(L_k,t_f))^2 + wV[f_n(L,t_f;\theta]\} \tag{11}$$

$$\begin{aligned} s.t. \quad & T_{\min} \le T(t) \le T_{\max} \\ & R_{\min} \le \frac{dT}{dt} \le R_{\max} \\ & C(t_f) \le C_{\max} \\ & m_{seed,\min} \le m_{seed} \le m_{seed,\max} \\ & \bar{L}_{seed,\min} \le \bar{L}_{seed} \le \bar{L}_{seed,\max} \\ & \sigma_{seed,\min} \le \sigma_{seed} \le \sigma_{seed,\max} \end{aligned} \tag{12}$$

where $\hat{\theta}$ is the nominal parameter vector. The seed distribution is considered to be described by a Gaussian probability distribution function with mean $\bar{L}_{seed}$ and standard deviation σ_{seed}. The optimization provided the optimal seed characteristics $\bar{L}^*_{seed} = 56\ \mu m$, $\sigma^*_{seed} = 12\ \mu m$ and amount $m^*_{seed} = 2.4\ g$. The temperature profile is given in Figure 1, together with the linear profile for comparison. For the linear profile the optimal seed characteristics were used as initial conditions. Figure 2 shows the microscopic images of the crystals obtained when the profiles in Figure 1 were implemented at a laboratory scale crystallizer. The entire evolution of the size distribution during the batch is given in Figure 3. It can be seen that the optimal operating policy results in a significant bias of the distribution toward large particle sizes. The schematic representation of the practical implementation of the approach is shown in Figure 5. The proposed control strategy involves two controllers: (i) a tracking controller that follows a reference trajectory in the phase diagram, and (ii) a supervising controller that adapts the reference to changing operating conditions. At near to optimal conditions, the operating curve is usually close to the nucleation curve and even small errors in the tracking can lead to spontaneous nucleation and compromised crystal quality. The feedback controller is designed that takes concentration and temperature

measurements and adjusts the jacket temperature so that a predefined (using on open-loop optimization design case) concentration vs. temperature operating is followed. The initial profile is predefined but it is adapted online using the model based predictive control approach. Concentration measurement is provided in the experimental implementation via ATR-UV/Vis coupled with robust chemometrics. Variations in operating conditions, such as quality and amount of seed, undesired secondary nucleation due to impurities in the system, disturbances in fluid dynamics, etc. require the adaptation of the operating curve both on-line and from batch to batch. The adaptation of the operating curve is especially important for complex organic molecules for which the metastable zone width might not be well defined and/or reproducible. The constrained optimization based nonlinear model predictive control strategy is used to estimate dynamic changes in shape and crystal size distribution.

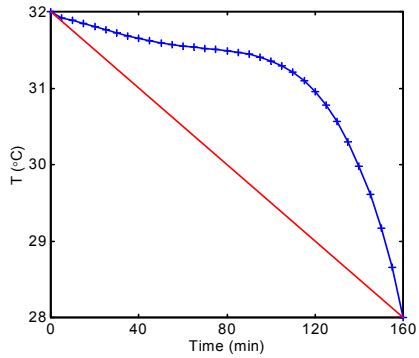

Fig. 1. The resulted optimal temperature profile (continuous line with plusses) and the linear cooling profile (dashed line).

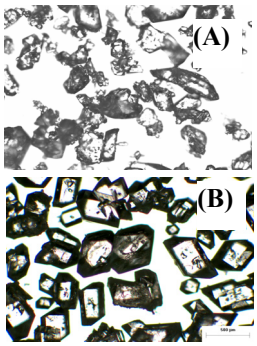

Fig. 2. Microscopic images of the crystal products obtained with linear (A) and optimal cooling (B), using the optimal seed in both cases.

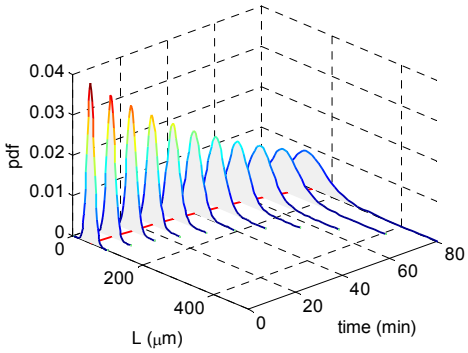

Fig. 3. Evolution of the pdf along the whole batch for case B.

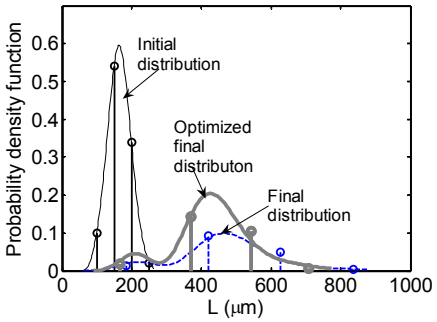

Fig. 4. CSD in the case of controlled and uncontrolled agglomeration.

In the second case study the agglomeration is modeled by considering and hydrodynamic agglomeration kernel $\beta = (L_i + L_j)^3$. An optimization problem similar to (10) is formulated but using the turbulent kinetic energy as optimization variable.

Figure 4 illustrate the results of the fluid dynamics optimization. The PBM with the agglomeration kernel is solved using the QMOM with four quadrature points, represented as bars on Figure 4. The distribution is reconstructed from the moments using a modified Gamma distribution with fourth order orthogonal Laguerre polynomials. In both cases bimodal distribution is obtained. The optimized final distribution shows significantly less agglomeration. In this case a perfectly mixed tank is considered with uniform kinetic energy in the volume. Current research considers the use of multi-compartmental model in conjunction with off-line CFD simulation to estimate the distribution of turbulent kinetic energy for optimized mixing conditions.

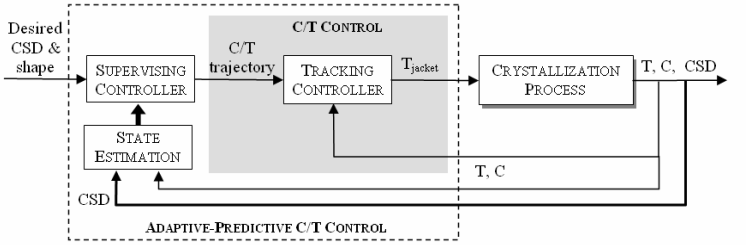

Fig. 5. Architecture for robust control of crystal habit and shape of CSD for batch cooling crystallization.

4. Conclusions

A robust optimization based control algorithm is described, which is able to design crystalline product properties, via optimization of cooling profile, seed properties or hydrodynamics. The approach provides robust performance by taking the parametric uncertainties into account in a distributional multi-objective optimization framework. The crystallization model is solved using a combination of method of characteristics and standard method of moments or quadrature method of moments, leading to a computationally very efficient approach which can be used even in real time. The two level control strategy which includes at the lower level a supersaturation controller and a model based control on the higher level was implemented on a laboratory scale crystallizer. Both the simulation and experimental results illustrate the advantages of the proposed crystallization control approach.

Acknowledgements
The author would like to acknowledge the financial support from the Engineering and Physical Sciences Research Council (EPSRC) UK, project EP/E022294/1.

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