Control of continuous mixed solution mixed product removal crystallization processes

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In this paper continuous mixed solution mixed product removal (MSMPR) crystallization is considered. This process has been studied well, however, different aspects, in particular, process modeling, monitoring and control remain challenging. Within this paper we will present a new approach for online measurement of the crystal size distribution. Furthermore, unscented Kalman filtering is applied to overcome biased concentration measurement. Finally, a discrepancy-based control is applied to continuous MSMPR crystallization and its closed-loop performance is evaluated.

Keywords: crystallization monitoring, mixed solution mixed product removal crystallization, nonlinear control

1 Introduction

Crystallization is an important separation and purification process used to produce different solid materials from liquids in chemical, food and pharmaceutical industries. It allows to adjust such properties as crystal size, shape, polymorphic form and purity [1]. Control of the product quality as a whole, in most cases expressed in terms of its crystal size distribution (CSD), is difficult but worthwhile and requires both an online monitoring of this product quality and detailed knowledge of the considered process [2]. CSD affects product dissolution behavior, bioavailability and can facilitate downstream processing, so its adjustment has a strong influence on product quality and production performance.

In recent years, interest in continuous manufacturing grew dramatically. Within this field, continuous mixed solution mixed product removal (MSMPR) crystallization is a powerful approach. The main feature of the continuous MSMPR crystallization is a constant solution feed and a constant vessel content withdraw, which yields to the improvement of product quality and production rates, compared to a similar batch operation. In this paper continuous MSMPR crystallization modeling, online monitoring and control problems are considered. Image processing techniques are well tested in application to crystallization processes: Canny edge detector [3], model-based recognition [4], genetic-algorithm-based restoration from axis-length distribution (ALD) [5], sufficient image processing rate was reached for online operation using multiprocessing system [6]. In [7] it is claimed that realization in Matlab by Mathworks shows good quality, but remains sluggish. Image processing is a promising approach for online CSD measurement, but the mentioned imaging systems require sophisticated hardware and high computational power, so a new embedded approach will be discussed. During experiments an issue with concentration measurement was observed: measurement bias caused by crystal growth on the probe. One straightforward approach to reduce or even overcome this undesired phenomenon may be to alter the probe location within the tank or to change process conditions. Alternatively, model based state estimation techniques, e.g. unscented Kalman filtering (UKF) can be applied to reconstruct the solute concentration from the biased measurement [8]. Acquired and reconstructed measurements of the CSD and the concentration can now be used to design controls and operate the process in a desired way.

In order to control the CSD different strategies have been proposed including robust control [9], [10], [11], C-control [12], decentralized PID and nonlinear model predictive control (NMPC) [13], direct nucleation control [14]. A Lyapunov-function-based approach called discrepancy-based control was presented in [15], which was later generalized for particle systems [16]. In contrast to linearization-based control techniques, discrepancy-based control (DBC) considered in this contribution is applied to nonlinear model taking system nonlinearities into account. The general structure of the system including plant measurement, state estimation and control subsystems is shown in Fig. 1.

((Figure 1))

2 Mathematical modeling

Besides sophisticated experimental work, mathematical modeling of the process is necessary to obtain a thorough understanding of crystallization processes [17]. Here, the population balance modeling (PBM) approach [18] is used. We consider contents of the crystallizer to be well-mixed. Crystallization is governed by growth and secondary nucleation phenomena. Growth rate is assumed to be size-independent. Nucleating crystals have size L_{min} [19]. Dynamics of the crystal size distribution is described by the following population balance equation (PBE)

$$\frac{\partial n(L,t)}{\partial t} + G(t)\frac{\partial n(L,t)}{\partial L} = -\frac{n(L,t)}{\tau_v}, \tag{1}$$

where $n(L,t)$ is the crystal size distribution, t is time, L is characteristic length of crystal, $G(t)$ is the growth rate and τ_v is the residence time. Initial condition is

$$n(L, t_0 = 0) = n_0(L) \tag{2}$$

and boundary condition is

$$n(L_0 = L_{min}, t) = \frac{B(t)}{G(t)}, \tag{3}$$

where nucleation is governed by

$$B(t) = K_b (S(t) - 1)^b \mu_3(t) \tag{4}$$

with nucleation kinetics parameters K_b and b. Crystal growth is characterized by the following growth rate

$$G(t) = K_g \exp\left(\frac{-E_{A,g}}{R_{gas} T_v(t)}\right)(S(t) - 1)^g \tag{5}$$

with growth kinetics parameters K_g and g, activation energy $E_{A,g}$, gas constant R_{gas}, vessel temperature $T_v(t)$ and supersaturation $S(t)$

$$S(t) = \frac{c_v(t)}{c_{sat}(t)}, \tag{6}$$

where the equilibrium concentration $c_{sat}(t)$ is approximated as a polynomial:

$$c_{sat}(t) = \sum_{i=0}^{4} K_i (T_v(t))^i. \tag{7}$$

The properties of the modeled substance – KDP (monopotassium phosphate): growth and nucleation kinetics as well as solubility parameters shown in Table 1 were evaluated experimentally using methodology described in [20, 21].

((Table 1))

The liquid phase concentration dynamics is governed by

$$\frac{dc_v(t)}{dt} = \frac{1}{\tau_v}\left(c_{v,f} - c_v(t)\right) - \frac{3k_V \rho_s G(t)}{V_v \rho_v}\mu_2(t), \tag{8}$$

where $c_{v,f}$ is the feed concentration, k_V is the volumetric shape factor, ρ_s is the solid phase density, V_v is the total vessel contents volume, ρ_v is the liquid phase density and $\mu_2(t)$ is the second moment of the CSD. Arbitrary moments can be described by the moment transform

$$\mu_i(t) = \int_{L_{min}}^{\infty} L^i n(L, t)\, dL \tag{9}$$

with corresponding dynamics

$$\frac{d\mu_i(t)}{dt} = B(t)L_{min}^i + iG(t)\mu_{i-1}(t) - \frac{1}{\tau_v}\mu_i(t). \tag{10}$$

3 Online CSD measurement

Feedback control is based on process monitoring, so acquisition of representative data is crucial for efficient control. The proposed hardware design is a pragmatic combination of an online microscope and a low-cost single-board computer (Raspberry Pi by the Raspberry Pi foundation). Such system can be mounted on the flow-through cell and form a noninvasive online embedded video microscopy tool. Particle flow orients particles with bigger facet toward the microscope, therefore analyzed shots represent characteristic lengths of crystals. Image processing techniques are well tested in application to crystallization processes: Canny edge detector [3], model-based recognition [4], genetic-algorithm-based restoration from axis-length distribution (ALD) [5], sufficient image processing rate was reached for online operation using multiprocessing system [6]. In the contribution, the algorithm suggested in [22] is coded in Python programming language using OpenCV library.

Let $f(x, y)$ represent a 2D image, with coordinates x and y. First step for edge detection is smoothing and noise removal with Gaussian function

$$G_{filt}(\sigma) = \exp\left(\frac{-x^2 + y^2}{2\sigma^2}\right), \tag{11}$$

where σ is the standard deviation of Gauss kernel:

$$f_{filt}(x, y) = G_{filt}(\sigma) * f(x, y). \tag{12}$$

In the next step of Canny edge detection algorithm, the gradient $\nabla f(x, y)$ is calculated over the filtered image $f_{filt}(x, y)$:

$$\nabla f(x, y) = \begin{pmatrix} \frac{\partial f_{filt}(x, y)}{\partial y} \\ \frac{\partial f_{filt}(x, y)}{\partial x} \end{pmatrix}. \tag{13}$$

Therefore, edge gradient $F(x, y)$ and direction $\Theta(x, y)$ can be determined:

$$F(x, y) = \sqrt{\left(\frac{\partial f_{filt}(x, y)}{\partial x}\right)^2 + \left(\frac{\partial f_{filt}(x, y)}{\partial y}\right)^2}, \tag{14}$$

$$\Theta(x, y) = atan\left(\left(\frac{\partial f_{filt}(x, y)}{\partial x}\right)^{-1} \frac{\partial f_{filt}(x, y)}{\partial y}\right). \tag{15}$$

Further analysis is called non-maximum suppression. Gradient value is analyzed for local maxima in gradient and antigradient directions and marked as an edge, otherwise pixels are marked as background and thus set to zero. To robustify results double threshold filtration should be applied. The idea is to ignore low gradient values and keep high values, so F_{low} and F_{high} should be defined. Pixel $f_p(x_p, y_p)$ is treated as strong edge if $F(x_p, y_p) > F_{high}$, weak edge if $F_{low} < F(x_p, y_p) < F_{high}$, otherwise suppressed. Weak edge pixels are then tested for neighborhood of strong edge pixels. In positive case, they are kept as an edge, otherwise it is suppressed. It is reasonable to normalize threshold parameters as median f_{median} over the whole image and variance v. Therefore $F_{low} = f_{median}(1 - v)$, $F_{high} = f_{median}(1 + v)$. The crystal size distribution is thus an array of circle diameters corresponding to detected edges. Useful information about

crystal/solution ratio can be acquired by calculation of area ratio $\frac{V_{solid}}{V_v} = \frac{A_{solid}}{A_v}$, where A_{solid} is the area of crystals in the image, A_v is the crystal-free area, V_{solid} is the volume of crystals in the vessel and V_v is the volume of solution in the vessel. This relation can be used for exact calculation of the third moment such that $\mu_3 = \frac{A_{solid}}{A_v} V_v$.

The described image analysis software operates on Raspberry Pi hardware with the Raspbian operating system with an approximate rate of 10 frames per second (fps). For flow-through cell design such rate represents data well and makes online operation possible. An analyzed image example is shown in Fig. 2: the first image depicts an instance of taken images, the second image shows results of Canny edge detection and the third image represents resulting crystal size distribution, similar to the theoretically derived exponential distribution. The edge detection algorithm robustness is an important problem to discuss, especially if crystal/solution ratio is high. As seen in Fig. 2 (ii), crystal agglomerations, overlapping crystals and optical artifacts can influence the quality of the measurements, so the detection sensitivity should be thoroughly tuned for each setup.

((Figure 2))

4 State estimation

During the experiments crystal formation on the surface of the concentration sensor was observed resulting in a biased measurement of the solute concentration

$$c_{v,bias} = c_v + d \ . \tag{16}$$

Nevertheless, the unbiased concentration can be reconstructed using a model based state estimator. Therefore, an Unscented Kalman Filter (UKF) [8] was implemented, which is also used to estimate the bias *d*. Here, it is sufficient to include the dynamic equations of the first four moments of the CSD according to (10) instead of the full PBM (1). The overall UKF algorithm is implemented discrete time and the corresponding dynamics for the estimation of the states and the bias is given by

$$x(t_{k+1}) = \begin{pmatrix} \mu_0(t_{k+1}) \\ \mu_1(t_{k+1}) \\ \mu_2(t_{k+1}) \\ \mu_3(t_{k+1}) \\ c_v(t_{k+1}) \\ d(t_{k+1}) \end{pmatrix} = x(t_k) + f(x(t_k), w(t_k))\,\Delta t, \tag{17}$$

$$f(x(t_k), w(t_k)) = \begin{pmatrix} B(t_k) - \dfrac{\mu_0(t_k)}{\tau_v} \\ B(t_k)L_{min} + G(t_k)\mu_0(t_k) - \dfrac{\mu_1(t_k)}{\tau_v} \\ B(t_k)L_{min}^2 + 2G(t_k)\mu_1(t_k) - \dfrac{\mu_2(t_k)}{\tau_v} \\ B(t_k)L_{min}^3 + 3G(t_k)\mu_2(t_k) - \dfrac{\mu_3(t_k)}{\tau_v} \\ \dfrac{1}{\tau_v}(c_{v,f} - c_v(t_k)) - \dfrac{3k_V\rho_s G(t_k)}{V_v\rho_v}\mu_2(t_k) \\ 0 \end{pmatrix} + w(t_k), \tag{18}$$

$$y(t_k) = (\mu_0(t_k), \mu_1(t_k), \mu_2(t_k), \mu_3(t_k), c_v(t_k) + d(t_k))^T + v(t_k). \tag{19}$$

Here, **w** and **v** denote the zero mean process and measurement noises with covariance matrices ***Q*** and ***R***. To evaluate the performance, artificial measurements were generated using the simulation of the idealized model Eq. (1) - (6) and the theoretical bias was implemented as

$$d(t) = -0.15\ c_v(t_0)\left(1 - \exp\left(-3 \cdot 10^{-4} t\right)\right). \tag{20}$$

Thereby, it is assumed, that the crystal layer on the probe is increasing up to a certain maximum thickness. The performance of the UKF is shown in Fig. 3. It can be seen that both, a good reconstruction of the unbiased solute concentration and estimation of the disturbance is obtained for different assumptions on the measurement noise. Even for a relative large noise, the estimation is reasonably accurate.

((Figure 3))

5 Discrepancy-based control

Shift from batch to continuous operation has high potential, but this task is not trivial, especially in pharmaceutical industry, where uniformity of properties is extremely important. The continuous MSMPR crystallization is a nonlinear distributed-parameter system, therefore control design is a challenging task. Different strategies have been proposed including robust control [9], [10], [11], C-control [12], decentralized PID and nonlinear model predictive control (NMPC) [13], direct nucleation control [14]. A Lyapunov-function-based approach called discrepancy-based control was presented in [15] and generalized to particle systems in [16]. This approach uses a generalized distance measure, discrepancy, and Lyapunov stability theory in order to design a stabilizing control law for the nonlinear infinite-dimensional model. The choice of the appropriate discrepancy is motivated by the physical insight. In contrast to conventional linearization-based approaches, the full nonlinear behavior and complexity of the plant can be taken into account.

Consider a dynamical system which satisfies Eq. (1) - (6). Control is designed for the third moment μ_3 as controlled variable and temperature in the vessel T_v as manipulated variable. Defining a discrepancy ρ based on the third moment

$$\rho = \mu_{3,set} - \mu_3 = \int_0^\infty L^3 (n_{set} - n) dL \tag{21}$$

with initial condition $\rho(t_0 = 0) := \rho_0$, the associate control Lyapunov candidate functional is given by

$$V = \frac{1}{2}\rho^2 = \frac{1}{2}\left(\int_0^\infty L^3 (n_{set} - n) dL \right)^2 , \tag{22}$$

which is continuously differentiable and positive definite. In order to guarantee closed loop stability its time derivative should be negative definite for a non-zero discrepancy ρ . Calculating the time derivative results in

$$\dot{V} = \rho\dot{\rho} = \int_0^\infty L^3 (n_{set} - n) dL \left(- \int_0^\infty L^3 \frac{\partial n}{\partial t} dL \right) . \tag{23}$$

Inserting the population balance Eq. (1) with nucleation term yields

$$\dot{V} = -\int_0^{\infty} L^3 (n_{set} - n) dL \left(-\int_0^{\infty} L^3 G \frac{\partial n}{\partial L} dL - \frac{1}{\tau_v} \int_0^{\infty} L^3 n \, dL + \int_0^{\infty} L_{\min}{}^3 B \, dL \right). \quad (24)$$

The condition of closed-loop exponential stability with respect to the discrepancy ρ is given by

$$\dot{V} = -2cV \ , \quad (25)$$

where c is the convergence rate, the only parameter to be tuned. As the manipulated variable T_v enters growth kinetics dependency in a complicated way, the crystal growth rate G will be used as a virtual control input u_{virt} . This is possible as only the growth rate is affected by the vessel temperature. Substitution of (22) and (23) into (24) and rearrangement with respect to the growth rate yields the virtual control law

$$u_{virt} = \frac{c\rho + \frac{1}{\tau_v} \int_0^{\infty} L^3 n dL - \int_0^{\infty} L_{\min}{}^3 B dL}{\int_0^{\infty} L^3 \frac{\partial n}{\partial L} dL} \ . \quad (26)$$

The temperature T_v can be derived from the virtual control input by solving the following nonlinear algebraic equation at each instance of time

$$u_{virt} = K_g \exp\left(\frac{-E_{A,g}}{R_{gas} T_v} \right) \left(\frac{c_v}{c_{sat}(T_v)} - 1 \right)^g \quad (27)$$

Closed-loop performance is shown in Fig. 4, the simulation parameters are presented in Table 2. Simulation of the feedback loop with the derived discrepancy-based control shows the expected exponential convergence with reasonable control effort. The presented control technique is compared with the PI-controller tuned according to the module optimum for a specific setpoint [23]. The tuning parameters of the controllers are shown in Table 3. Integral square error (ISE) is used as a performance indicator and the comparison is shown in Table 4. In Fig. 4 three scenarios with different setpoints are depicted: the first setpoint is $\mu_{3,set} = 2.6 \cdot 10^{-4} m^3$, the second is $\mu_{3,set} = 2.8 \cdot 10^{-4} m^3$ and the third is $\mu_{3,set} = 3 \cdot 10^{-4} m^3$. It is noticeable that linear control performance worsens as the setpoint drifts away from the linearization point, whereas DBC keeps decent performance in different regimes. In [24] it is claimed that the robustness of the controller towards substance properties uncertainty, in other words – plant-model

mismatch should be assured. To overcome such issue, the adaptive form of the DBC [25] should be considered.

((Figure 4))

((Table 2))

((Table 3))

((Table 4))

6 Conclusions

Within this paper important issues of continuous MSMPR crystallization were tackled: CSD online monitoring, state estimation and control, forming a general process control structure as in Fig. 1. Noninvasive online embedded video microscopy is an efficient, affordable and flexible tool to enhance crystallization monitoring. Suggested online monitoring reaches performance of approximately 10 fps, which allows to apply sophisticated control schemes based on solid state measurements. Noninvasive online embedded video microscopy can be used not only for CSD measurements, but for metastable zone detection or morphology analysis as well. Although, Canny edge detector allows to tackle some drawbacks of video microscopy, use of different schemes such as Otsu's binarization or watershed transform should improve the overall performance: reduce computational cost, expand possible crystal density range, alleviate overlapping crystals detection, avoid false positive detections. During experiments concentration measurement issue was retrieved and overcome by unscented Kalman filtering which allowed reconstruction of solute concentration from biased measurement. It shows good performance and overcomes emerging measurement noise. Control design for continuous MSMPR crystallization is a challenging task due to nonlinear and distributed-parameter behavior. This motivated the application of discrepancy-based control design. System simulation show exponential convergence according to Lyapunov stability theory. Measurements based on different algorithms, their verification and validation is the next iteration of research as well as implementation of the designed state estimator and controller.

Symbols used

Symbols

$n(L,t)$	[# m^{-1}]	crystal size distribution
t	[s]	time
L	[m]	characteristic crystal length
L_{min}	[m]	nucleus size
$G(t)$	[m s^{-1}]	growth rate
$n_0(L)$	[# m^{-1}]	initial seeding
$B(t)$	[# s^{-1}]	nucleation rate
K_b, b, K_g, g	[-]	kinetics parameters
$E_{A,g}$	[J mol^{-1}]	growth activation energy
R_{gas}	[J K^{-1} mol^{-1}]	gas constant
K_i	[-]	interpolation factors
$c_v(t)$	[g g^{-1}]	liquid phase concentration
$c_{sat}(t)$	[g g^{-1}]	equilibrium concentration
$c_{v,f}$	[g g^{-1}]	feed concentration
$S(t)$	[-]	supersaturation
$T_v(t)$	[K]	solution temperature
V_v	[m^3]	solution volume
k_V	[-]	volumetric shape factor
$f(x,y)$	[-]	image
x,y	[-]	Cartesian coordinates
$G_{filt}(\sigma)$	[-]	Gaussian function
$f_{filt}(x,y)$	[-]	filtered function
$\nabla f(x, y)$	[-]	image gradient
$F(x, y)$	[-]	gradient magnitude
$\Theta(x, y)$	[-]	gradient argument
F_{low}, F_{high}	[-]	threshold values

$f_p(x_p,y_p)$	[-]	pixel intensity
f_{median}	[-]	median threshold value
V_{solid}	[m^3]	solid phase volume
A_{solid}	[m^2]	solid phase area
A_v	[m^3]	solution volume
$c_{v,bias}$	[g g^{-1}]	biased concentration
d	[g g^{-1}]	bias
w	6-by-1 vector	process noise
v	5-by-1 vector	measurement noise
Q, **R**	6-by-6 matrices	covariance matrices
x	6-by-1 vector	state vector
y	5-by-1 vector	output vector
n_{set}	[# m^{-1}]	size distribution setpoint
V	[m^6]	candidate Lyapunov functional
c	[-]	Tuning parameter
u_{virt}	[m s^{-1}]	virtual manipulated variable

Greek symbols

τ_v	[s]	residence time
σ	[-]	standard deviation
v	[-]	threshold variance
ρ_s	[kg m^{-3}]	solid phase density

ρ_v	[kg m^{-3}]	liquid phase density
μ_i	[m^i]	i-th moment
$\mu_{3,set}$	[m^3]	3rd moment setpoint
ρ	[m^3]	discrepancy

Sub- and superscripts

g	growth
b	nucleation/birth
min	minimal
set	setpoint
k	on the k-th step
0	at initial time moment
v	related to the solution in the vessel
s	related to the solid phase
filt	filtered

Abbreviations

MSMPR	mixed solution mixed product removal
CSD	crystal size distribution
PBM	population balance modeling
ALD	axis-length distribution
PID	proportional-integral-differential
PI	proportional-integral
NMPC	nonlinear model predictive control
DBC	discrepancy-based control
UKF	unscented Kalman filter

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Tables with headings

Table 1 – KDP kinetics and solubility

Variable	Value
K_g	5112597.405
g	1.2586921036
$E_{A,g}$	69859.933026
K_b	26856478430.55499
b	4.235315794045159
K_0	15.2361
K_1	0.2058
K_2	0.0101
K_3	-1.4506e-4
K_4	1.2292e-6

Table 2 – Process parameters and initial conditions

Parameter	Value
V_v	$0.026 \quad m^3$
ρ_v	$1140 \quad kg \quad m^{-3}$
k_V	0.7498
ρ_s	$2340 \quad kg \quad m^{-3}$
τ_v	$3120 \quad s$
$c_{v,f}$	$0.2757 \quad g \quad g^{-1}$
$T_v(0)$	$296 \quad .25 \quad K$
$c_{sat}(0)$	$0.2396 \quad g \quad g^{-1}$
$c_v(0)$	$0.2613 \quad g \quad g^{-1}$
$B(0)$	$250 \quad .4878 \quad \# \quad s^{-1}$
$G(0)$	$1.1973 \quad \cdot 10^{-7} \quad m \quad s^{-1}$
n(L,0)	$\frac{B(0)}{G(0)} \exp\left(-\frac{L}{G(0)\tau_v}\right)$

Table 3 – Control parameters

Control parameter	Value
DBC: convergence rate c	0.001
PI-control: proportional factor	-48000
PI-control: integral factor	-3.86

Table 4 – Control performance, setpoints and initials

Controller	$\mu_{3,set}$	ISE
DBC	$2.6 \cdot 10^{-4} \, m^3$	0.0162
PI-control	$2.6 \cdot 10^{-4} \, m^3$	0.0175
DBC	$2.8 \cdot 10^{-4} \, m^3$	0.0370

PI-control	$2.8 \cdot 10^{-4} m^3$	0.0707
DBC	$3 \cdot 10^{-4} m^3$	0.0578
PI-control	$3 \cdot 10^{-4} m^3$	0.1237

Figure legends

Figure 1: General structure of image processing, unscented Kalman filter (UKF) and discrepancy-based control (DBC)

Figure 2: Crystal size measurement procedure: (i) acquired image, (ii) edge detection results, (iii) crystal size histogram

Figure 3: State estimation results for three scenarios: low noise - (i) ideal, biased and reconstructed measurement, (ii) estimation of bias compared to "real" bias; medium noise - (iii) ideal, biased and reconstructed measurement, (iv) estimation of bias compared to "real" bias; large noise - (v) ideal, biased and reconstructed measurement, (vi) estimation of bias compared to "real" bias;

Figure 4: MSMPR control simulation for three scenarios: $\mu_{3,set} = 2.6 \cdot 10^{-4} m^3$ - (i) manipulated variable T_v, (ii) controlled variable μ_3; $\mu_{3,set} = 2.8 \cdot 10^{-4} m^3$ - (iii) manipulated variable T_v, (iv) controlled variable μ_3; $\mu_{3,set} = 3 \cdot 10^{-4} m^3$ - (v) manipulated variable T_v, (vi) controlled variable μ_3

Short text for the table of contents section

TBD