A Stochastic Approach for Anti-Solvent Addition Policy in Crystallization Operations: An Application to a Bench-Scale Fed-Batch Crystallizer

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Abstract: This work aims a stochastic approach for the calculation of robust anti-solvent addition policies for controlling the mean crystal size (MCS) in fed-batch crystallization operations. The proposed strategy is based-on a non-structured population balance where uncertainties associated with the start-up condition and random fluctuations along the fed-batch operation can be taken into account in a very natural fashion. We include and quantify the effect of the uncertainties by embedding a deterministic crystal growth model into a Fokker-Planck equation (FPE) resulting in a stochastic model for the MCS dynamics. This approach uses the Generalized Logistic equation (GLE) that has an adequate mathematical structure that suits the dynamic characteristic of the crystal growth. Thus, the numerical solution of the FPE provides the most likely MCS evolution for a given anti-solvent flow-rate. The effect of the anti-solvent is incorporated into the parameters of the FPE. The parameters of the FPE are computed as linear piece-wise interpolating functions of the anti-solvent flow-rate. The strategy uses a PID-like regulator in closed-loop fashion with the FPE to compute the anti-solvent addition flow-rates for different set-point targets in the MCS. In order to validate the stochastic model and assess the merits of the proposed strategy, the crystallization of sodium chloride in water using ethanol as anti-solvent is performed in a bench-scale fed-batch crystallizer. The implementation of the calculated anti-solvent policies resulted in a good control of the MCS despite modelling mismatch and uncertainties present during the crystallization operation.

Keywords: Anti-Solvent; Crystallization; Fokker-Planck Equation; Mean Crystal Size; Stochastic.

1. INTRODUCTION

The design of chemical plants endeavors to build equipment that preferably content hazards and make possible the transformation and separation of materials. It also attempts to harness the impact of apparently disordered and erratic phenomena (*e.g.* turbulent flow, pressure and temperature fluctuations, measurement noise, etc.). Fluctuations are a very common element in a large number of chemical, biological and physical phenomena. Practically, all systems are subjected to complicated external or internal influences that are not fully known and that are often termed noise or fluctuations. However, if a sufficiently long record of noisy measurement is analyzed, it may admit a statistical description. This means that it is possible to estimate the probability or likelihood that the process variable will attain in some specified range of values (Feigenbaum, 1980; Risken, 1984).

The study of stochastic system as the Brownian motion resulted in the Fokker-Planck equation (FPE). The FPE is just an equation of motion for the distribution function of fluctuating macroscopic variables. The FPE deals with those fluctuations of systems which stem from many tiny disturbances, each of which changes the variables of the system in an unpredictable but small way. The FPE provides a powerful tool with which the effects of fluctuations close to transition points can be adequately treated and that the approaches based on FPE are superior to other approaches based on Langevin equations (LE). The FPE plays an important role in chemical and biological processes that involve noise.

For many practical applications it is required to have simplified models that group the complexity behind a natural phenomenon and its interactions with its surroundings. For a dynamic system, it means of a set of deterministic differential equations with semi-empirical parameters. When studying chemical processes, these models are the core element for the design of all model-based control and optimization strategies. However, extra care is needed to take into account the no modeled dynamics and unknown exogenous disturbances acting on the process. The FPE is an interesting approach to introduce the robustness feature to the design of prediction, control and optimization tools.

This work describes a novel stochastic approach for the robust prediction of the mean crystal size (MCS) in a bench-scale fed-batch crystallization unit where anti-solvent is added to speed-up the crystal formation process. The crystal growth is modeled by a classic logistic equation of common use in theoretical ecology (May and McLean, 2007; Grosso et al., 2007). In a different fashion, the use of FPE for a monomer particle growth can be found in the literature (Matsoukas and Yulan, 2006). Unknown dynamics, internal and external fluctuations and sensitivity to initial conditions can be taken into account by embedding the logistic equation in the FPE.

2. Mean Crystal Size Estimation for an Anti-Solvent Aided Crystallization Process

Crystallization is a physical process for solid-liquid separation where the solid (solute) is dissolved in the solvent (liquid). The driving force in crystal formation is the super-saturation. The super-saturation condition establishes the thermodynamic equilibrium for the solid-liquid separation and it can be affected by cooling and evaporation. The super-saturation can be also induced by addition of precipitant or anti-solvent to the solution. The anti-solvent reduces the solubility of the solute in the original solvent resulting in super-saturation. The anti-solvent aided crystallization is an advantageous technique of separation where the solute is highly soluble or heat sensitive.

2.1 Mathematical Model

The development of rigorous mathematical models describing the dynamic of crystal growth in crystallization processes are based-on population balances. The idea of population balances has been widely used in theoretical ecology and extended to the modeling of particulate systems in chemical engineering. The population balances can be either structured or unstructured models.

At the core of the structured population dynamics, the number of crystals in a fed-batch crystallizer is increased by nucleation and decreased by dissolution or breakage. Structured population balances models provide detailed information regarding the crystal size distribution in the crystallization unit. However, they demand a great deal of knowledge on the complex thermodynamic associated with the solute and solvent properties to be adequately incorporated in the population balances. Some important contributions in this subject have been reported in the literature (Worlitschek and Mazzotti, 2004; Nagy et al. 2007; Nowee et al., 2007).

Here, we introduce a simple unstructured population model, where the crystals are classified by their size, L. The growth of each individual crystal is supposed to be independent by the other crystals and is governed by the same deterministic model. In order to take into account the growth fluctuations and the unknown dynamics not captured by the deterministic term, a random component can be introduced (Gelb, 1988). The stochastic model can thus be written as a Langevin equation of the following type:

$$\dot{L} = f(L;\vartheta) + \eta(t) \qquad (1)$$

In Equation 1, $f(L;\vartheta)$ is the expected rate of growth of L (the deterministic model introduced below), L is the size of the single crystal, t is the time, ϑ is the vector parameter defined in the model, and $\eta(t)$ is a random term assumed as Gaussian additive white noise:

$$E[\eta(t)] = 0$$
$$E[\eta(t)\eta(t+\tau)] = 2D\delta(\tau) \qquad (2)$$

Where D is the additive noise intensity. Equation 1 implies that the crystal size L behaves as a random variable, characterized by a certain probability density function (PDF) $w(L,t)$ depending on the state variables of the system, i.e. the size L and time t. Incidentally, it should be noted that one can regard the probability density $w(L,t)$ as the relative ratio of crystals having a given dimension L, in the limit of infinite observations. Thus, from a practical point of view, it coincides with the Particle Size Distribution experimentally observed.

The new random variable thus can be described in terms of its probability density distribution, $w(L,t)$, at any instant of time t and should follow the linear Fokker-Planck Equation, FPE:

$$\partial_t w + \partial_L [f(L;\vartheta(u))w] = D(u)\partial_{LL} w \qquad (3)$$

along with the boundary conditions:

$$f(0)w(0,t) - D(u)\partial_L w(0,t) = 0 \qquad (4a)$$

$$\partial_L w(\infty,t) = 0 \qquad (4b)$$

The reflecting boundary condition in Equation 4a ensures that the elements of the population will never assume negative values, whereas Equation 4b ensures the decay condition on $w(L,t)$ as L goes to infinity, for any time.

The diffusion coefficient D determines the random motion of the variable L that takes into account the fluctuation in the particle growth process (Randolph and Larson, 1988; Olesen et al, 2005).

Regarding the deterministic part of the model, our purpose is to choose a model as simple as possible, with a parsimonious number of adjustable parameters. To this end, the Generalized Logistic equation (Tsoularis and Wallace, 2002), is possibly the best-known simple sigmoidal asymptotic function used to describe the time dependence of growth processes in an unstructured fashion:

$$f(L;\vartheta) = rL^{\alpha} [1-(L/K)^{\beta}]^{\gamma} \qquad (5)$$

In Equation 4, L is the size of the single crystal, the crystal growth rate r and the equilibrium mean crystal size K are considered constant for each experimental condition and they are supposed to be only dependent on the anti-solvent flow rate. Moreover, α, β and γ are positive real numbers that regulate the shape of the growing curve. Hereafter we will consider the simple case with $\alpha=\beta=\gamma=1$. With these assumptions, the present growth model can be regarded as the simplest model taking into account mild nonlinearities. In spite of this simplicity, this model provides the main qualitative features of a typical growth process: the growth follows a linear law at low crystal size values and saturates at a higher equilibrium value.

Finally the evolution in time of the probability density is described in terms of a linear, partial differential equation depending on the parameters r (linear Malthusian growth

rate), K (crystal size asymptotic value) and D (diffusivity), that are assumed to depend on the feeding conditions. This functionality is achieved by linear interpolation of the parameters as a function of the different anti-solvent flow rates. This parameterization with the anti-solvent flow rate allows the merger of multiple models for different operating regimes to a single model in the all operating envelop.

It is worth to stress out that the synergy between unstructured population balances and the Fokker-Planck equation results in structured-like population balances.

3. Experimental Validation

For parameter estimation and model validation purposes, three different anti-solvent flow-rates were implemented. All experiments were carried in a bench scale crystallizer which was kept at a fix temperature. Only purified water, regent grade sodium chloride (99.5%) and absolute ethanol (99.9%) were used. The experimental set-up and procedure are described as follows.

3.1 Experimental Set-up

The experimental rig is made up of one litre glass, cylindrical crystallizer submerged in a temperature controlled bath. The temperature in the bath is measured using an RTD probe which is wired up to a slave temperature control system capable of heating and cooling. In similar fashion, the anti-solvent addition is carried out by a slave peristaltic pump. The master control is performed by a Distributed Control System (Honeywell® DCS) which is wired up to the slave temperature and flow-rate controllers respectively. The desired set-points are calculated at the master controller. All relevant process variables are archived in the DCS system. In addition there is a particle size analyzer (Mastersizer® 2000) for the determination of the mean and crystal size distribution along the experiment. The mean crystal sizes and their distribution are also verified by visual inspection using a digital camera mounted in a microscope. The captured images are then processed by means of sizing computer software (Amscope®).

3.2 Experimental Procedure

At the start-up condition, the crystallizer is loaded with an aqueous solution of *NaCl* made up of *34 g* of NaCl in *100 g* of water. The temperature is kept at $25°C$. Then ethanol was added to the aqueous NaCl solution using a calibrated peristaltic pump. Along the operation, *5 mL* samples were taken in an infrequent fashion. The samples are then measured off-line using the particle size analyzer. Also, part of the sample was filtered over filter paper and then dried in an oven at $50°C$ for farther visual inspection.

3.3 Parameter Estimation

The three parameters for the Fokker-Planck equation were estimated based-on experimental data obtained by monitoring the mean size distribution for different flow rates of anti-solvent. For every operating condition, that is, anti-solvent flow rate, a set of parameters $\vartheta = \{r, K, D\}$ is estimated using a nonlinear least-square algorithm. The values for the estimated parameters are given in the Table 1.

u (mL/min)	r (1/h)	K (μm)	D (μm² /h)
0.82	1.83	131.51	568.12
1.64	1.15	132.03	287.48
3.23	62.58	105.45	291.27

Table 1: Estimated parameters for the different operating conditions for the constant values $\alpha = 1$, $\beta = 1$ and $\gamma = 1$.

3.4 Model Validation

In order to assess the prediction capabilities of the mathematical model based on the Fokker-Planck equation, the model predictions are compared with the reported experimental data within a valid range for the different operating conditions. It implies that the parameterization of the crystal growth rate, the free crystal size and the diffusivity coefficient with the anti-solvent are only reliable within the experimental range. The numerical solution of the mathematical model based on the Fokker-Planck equation requires an initial condition for the crystal size distribution. However, the initial condition requires information on crystal sizing. Observing the experimental data (Figure 1), the first available data value is at $t_0 = 0.1 h$ (new origin), where the mean crystal size is around $L_0 = 92 \, \mu m$ for anti-solvent flow rate. In order to take into account the uncertainty associated with this condition, a standard deviation $\sigma_0 = 30 \, \mu m$ typical for this measurement is then assumed. Once the initial and boundary conditions are posed, the partial differential equation is then solved using a collocation method. The number of collocation knots $n = 300$ and they are chosen as the roots of the Chebyshev polynomial of degree "n" where the solution domain is $L \in [0, \ell]$ with $\ell = 210 \, \mu m$ a sufficient high value. Note that a different set of data values were used for parameter estimation. Thus, the numerical solution of the Fokker-Planck equation (2-3) by the collocation methods provides the predictions for the mean crystal size by computing the first moment of the distribution (see Figure 1).
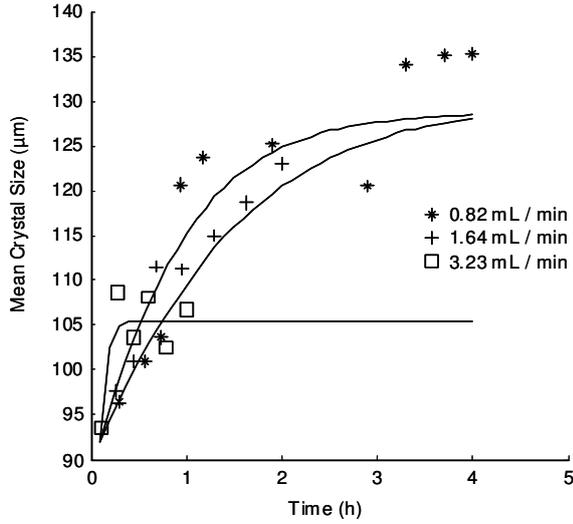
Figure 1: Model validation of the mean crystal size for different anti-solvent flow rates. Experimental results at low (*), medium (+) and high (□) anti-solvent flow rates. The three-parameter model based-on the Fokker-Planck equation predicts the dynamic behaviour of the mean crystal size growth for all anti-solvent flow rates (solid lines).

4. Calculation of the Robust Anti-Solvent Flow Rate Profile

4.1 Problem Formulation

Let us consider without loss of generality that the mean crystal size growth dynamics in an anti-solvent aided process is given by the following forced deterministic equation:

$$\dot{\mu}_L = F(\mu_L, u) \qquad (6)$$

Where the forcing input (anti-solvent flow rate) is constrained, that is, $u \in [u^-, u^+]$. We say that the solutions of (6) in the time interval $t \in [0, t_0]$ for any input u and any given uncertain initial condition $\mu_L(0) \neq 0$ generates trajectories which at $t_0 > 0$ lie around a nominal value L_0, that is,

$$\mu_L(t_0) = L_0 \pm \Delta_0, \forall t_0 > 0 \qquad (7)$$

It means that regardless what the input is, the effect of the uncertainty in the initial condition is propagated to another point $\mu_L(t_0)$ in the trajectory (7), where a nominal mean crystal size L_0 is associated with an uncertainty Δ_0. It is advantageous since it is then possible to choose a new initial time origin at the point t_0, which coincides with experimental data value that helps to quantify the values for L_0 and Δ_0. Thus, the new initial condition at t_0 is still uncertain but it can be characterized and incorporated to our mathematical description of the problem.

The robust anti-solvent flow rate profile for the mean crystal size distribution is calculated using a hybrid strategy that requires engineering insight and process knowledge. The strategy involves a piece-wise function (8), a regulator-like (PI) algorithm (9), and a saturation function (10).

$$u = \begin{cases} u^+, \text{if } t \leq t_0 \\ \zeta(v), \text{otherwise} \end{cases} \qquad (8)$$

$$\dot{v} = \kappa_1 \dot{\mu}_L + \kappa_2 (\mu_L - L_r), v(t_0) = u^+ \qquad (9)$$

$$\zeta(v) = \begin{cases} u^-, \text{if } v \leq u^- \\ u^+, \text{if } v \geq u^+ \\ v, \text{otherwise} \end{cases} \qquad (10)$$

From the actual starting-up condition at $t = 0$ to a chosen origin $t_0 > 0$, the anti-solvent flow rate is maintained constant at its maximum value u^+. It has been experimentally observed that the anti-solvent addition at the initial stage of the crystallization process promotes nucleation and speeds up the mean crystal size growth rate. Then, from time $t > t_0$ onwards the anti-solvent addition must be controlled in order to reach a desirable mean crystal size L_r. It is achieved by using a dynamic velocity-like regulator algorithm which is tuned selecting arbitrary values for the constants κ_1 and κ_2. Since the anti-solvent flow rate is constrained, it is necessary to include a saturation function to limit the control action within its physical range. It is important to highlight that velocity-like regulator with initial condition $v(t_0) = u^+$ introduces a bump-less transition from the saturation state. Also, the volume of spent anti-solvent at any time can be calculated using (11). The constant value "60" is the conversion factor for the anti-solvent flow rate from mL/min to mL/h.

$$V = 60[u^+ t_0 + \int_{t_0}^{t} u(\xi) d\xi] \qquad (11)$$

It is important to remark that the strategy can be used either as a size-regulator, if the mean crystal size μ_L is a real-time available measurement or as tool to calculate an *off-line robust trajectory* for the anti-solvent addition. Due to its simplicity, this strategy can be easily implemented.

4.2 Simulation and Experimental Validation of Anti-Solvent Addition Policy

We next use numerical simulations and experimental validation to assess the closed loop performance of the anti-solvent addition strategy proposed for this specific crystallization process. The simulation parameters are given in Table 2. Since the experimental data is constrained to a certain operating window, the calculated profile is also limited to this operating range. The anti-solvent addition strategy was tested within the validity range of the experimental data and targeting a medium mean crystal size. The initial condition is then represented as a Gaussian –like distribution with mean value $L_0 = 92 \mu m$ and standard deviation $\sigma_0 = 30 \mu m$ based-on the experimental information.

Parameter	Value
u^- (mL/min)	0.82
u^+ (mL/min)	3.23
κ_1 (mL/h·μm)	0.0052
κ_2 (mL/h²·μm)	-0.0015
L_0 (μm)	92.0
σ_0 (μm)	30.0
ℓ (μm)	210.0
t_0 (h)	0.1
Δt (h)	0.1

**Table 2:** Simulation parameters for the assessment of the anti-solvent addition strategy.
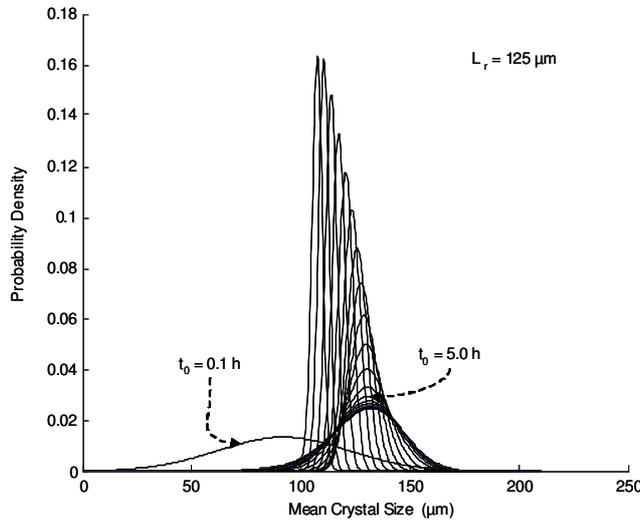
Figure 2: Propagation of the probability density.

Figure 2 depicts the time evolution of the time evolution of the probability density function as function of time for $L_r = 125\,\mu m$. For sake of brevity only one value is reported here. For a set point of $L_r = 125\,\mu m$ (medium size), the crystal growth rate is alike the previous case, however the anti-solvent flow rate is cut down to an even lower flow rate. It makes clear that the transition between high and low concentration of anti-solvent in the solution promotes the crystal growth instead of the new crystal formation. Therefore, it results in larger crystal size. The volume of anti-solvent added to the crystallizer for a desired mean crystal sizes are calculated using (11) and it is 669.48 *mL* for medium crystal size. The calculation is based on 5.0 hours of operation. Note that the upper and lower prediction bounds for the mean size distribution (Figure 3) are wider at the start-up condition and its narrows when reaching the desired set-point value. The steady-state crystal size distribution suggests that at controlled conditions it is possible to have a very narrow mean size distribution for a given anti-solvent addition policy (Figure 4).
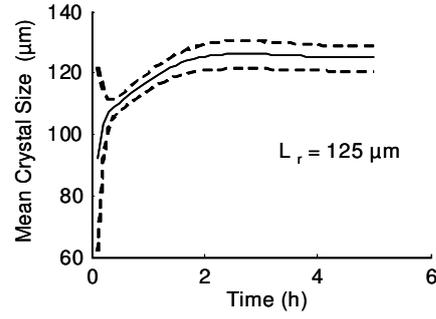
Figure 3: Predicted mean crystal size and its lower and upper bound.

The distribution indicates how disperse the experimental data is. The observed dispersion is incorporated in the diffusivity coefficient of the Fokker-Planck equation. It is envisaged that depending on the amount and quality of the experimental data, the diffusivity coefficient can be clearly related with the crystal size distribution and predicted by this modeling approach. Figure 5 shows the time evolution of the mean crystal size when the anti-solvent addition policy is implemented experimentally for a desired value of time evolution of the $L_r = 125\,\mu m$. The quantitative growth of crystal size can be seen in the Figures 6a to 6c. Note the size scale at the corner of every picture.
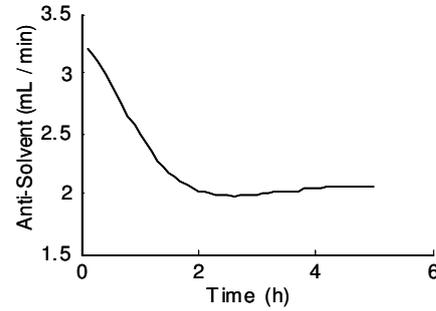
**Figure 4:** Anti-solvent addition policy for a desired mean crystal size of $L_r = 125\,\mu m$.
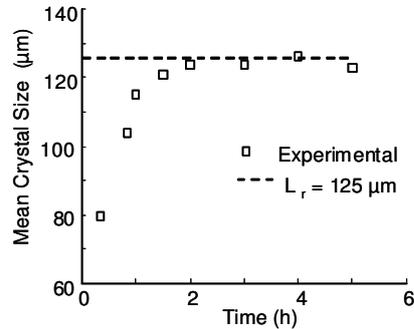
Figure 5: Mean crystal size evolution when the anti-solvent addition policy is implemented.

5. CONCLUSIONS

The hybrid strategy of using the Fokker-Planck Equation (FPE) and the PI-like regulator for the calculation of the anti-solvent addition policy has proved to be simple and still a powerful way to control the mean crystal size in a crystallization operation. It is envisaged that the FPE is a rather useful fashion to study systems with uncertain initial condition in dynamic systems. The initial uncertainty can be quantified and naturally included in the structure of the solution. Future work will be devoted to exploit the FPE approach for the determination of the mean crystal size and its distribution in cooling and anti-solvent aided crystallization.
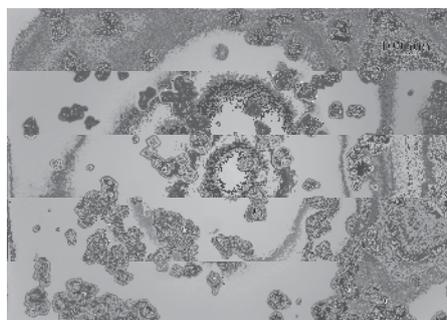
Figure 6.a $NaCl$ crystals at $t = 0.16\,h$
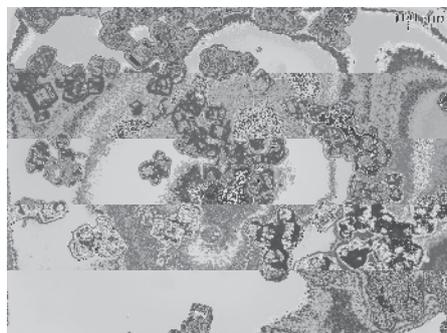
Figure 6.b $NaCl$ crystals at $t = 1\,h$
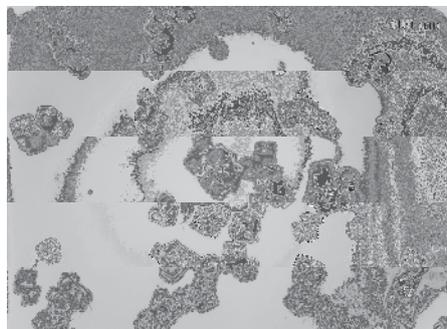
Figure 6.c $NaCl$ crystals at $t = 2\,h$

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