

A Stochastic Approach to Model Antisolvent Mediated Crystal Growth Processes

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A stochastic phenomenological model for the description of antisolvent crystal growth processes is here presented. The size of each crystal is supposed to be subjected to a geometric Brownian motion and its evolution in time is described in terms of a Fokker-Planck equation. A deterministic growth term is added to the model and is expressed as a simple logistic equation. A comparison with experimental data will be presented.

1. Introduction

Antisolvent aided crystallization is an advantageous technique of separation where the solute is highly soluble or heat sensitive. The driving force in crystal formation is the super-saturation that establishes the thermodynamic equilibrium for the solid-liquid separation.

The development of rigorous mathematical models describing the dynamic of crystal growth in crystallization processes is based-on population balances. 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; Nowee et al., 2008). In the present work we propose a simple unstructured population model, where the crystals are classified by their size and the growth of each individual crystal is supposed to be independent by the other crystals and is governed by the same deterministic model. In particular, a stochastic phenomenological model for the description of antisolvent crystal growth is derived and the time evolution of the crystal population is described through a Fokker-Planck Equation.

2. Mathematical Model

In the proposed model, the crystals are classified by their size, L and 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). This random component can be thought as a Geometric Brownian Motion, GBM, (Risken, 1996; Ross, 2003; Mantegna and Stanley, 2000) where the intensity of the fluctuations depends linearly by the crystal size. The stochastic model can thus be written as a Langevin equation of the following type:

$$\frac{dL}{dt} = \mu(L, t; \theta)L + L \eta(t) \quad (1)$$

In Equation 1, $\mu(L, t; \theta)$ is the expected rate of growth (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 i.e., $E[\eta(t)] = 0$ and $E[\eta(t)\eta(t+\tau)] = 2D\delta(\tau)$, 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) $\psi(L, t)$ depending on the state variables of the system, i.e. the size L and time t .

It should also be noted that, when the GBM assumption holds, the PDF is a lognormal distribution, at least in the limit case of constant μ value (Ross, 2003). When μ also depends on L , some (minor) distortions from the ideal lognormal case are however expected. This feature is qualitatively observed for many (although not all) crystalline substances (Eberl et al, 1990) and in the present case.

The Langevin Equation 1 can be further manipulated as follow:

$$\frac{1}{L} \frac{dL}{dt} = \mu(L, t; \theta) + \eta(t) = \frac{dy}{dt} = \mu(y, t; \theta) + \eta(t) \quad (2)$$

where the new variable $y = \ln L$ is introduced. The random variable, y , thus can be described in terms of its probability density distribution, $\psi(y, t)$, at any instant of time t and should follow the linear Fokker-Planck Equation, FPE (Risken, 1996):

$$\frac{\partial \psi(y, t)}{\partial t} = -\frac{\partial}{\partial y} (\mu(y, t; \theta)\psi(y, t)) + D \frac{\partial^2 \psi(y, t)}{\partial y^2} \quad (3)$$

The diffusion coefficient D determines the random motion of the variable y that takes into account the fluctuation in the particle growth process (Matsoukas and Lin, 2006). As it regards 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 Logistic equation is possibly the best-known simple sigmoidal asymptotic function used to describe the time dependence of growth processes in an unstructured fashion (c.f., Tsoularis and Wallace, 2002; Grosso et al., 2007), i.e.:

$$\mu(y, t; \theta) = ry \left[1 - \left(\frac{y}{K} \right) \right] \quad (4)$$

In Equation 4, y is the exponential of 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 depended on the anti-solvent flow rate. 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) Malthusian law at low crystal size values and saturates at a higher equilibrium value. Using the selected growth model, the FPE can be written as:

$$\frac{\partial \psi}{\partial t} = -\frac{\partial}{\partial y} \left(ry \left(1 - \frac{y}{K} \right) \psi \right) + D \frac{\partial^2 \psi}{\partial y^2} \quad (5)$$

along with the boundary conditions (Risken, 1996):

$$\begin{aligned} -f(y)\psi(y, t) + D \frac{\partial \psi(y, t)}{\partial y} &= 0 & \text{at } y = 0, \forall t \\ \frac{\partial \psi(y, t)}{\partial y} &= 0 & \text{as } y \rightarrow \infty \quad \forall t \end{aligned} \quad (6)$$

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. Indeed, the antisolvent crystallization kinetics is affected by the antisolvent feed rate and, the parameters appearing in the model can be finally related to these operating conditions.

The numerical integration of Equation 5 was accomplished by exploiting the routine DASPG, from IMSL, in order to solve the resulting implicit system of algebraic ordinary differential equations obtained by means of collocation on finite elements.

3. Experiments

The experimental data used in the present work are those reported in Nowee et al. (2008). In particular, four experiments were selected under three constant antisolvent feeding profiles – one experiment at a feedrate of 0.83 ml.min⁻¹, (low feed rates, hereafter we refer to this experiment as run A), two at a medium rate of 1.64 ml.min⁻¹ (run B) and one at a higher rate of 3.2 ml.min⁻¹ (run C). The first acquisition time, t_0 , for each run will be the initial condition used for the FP model calibration. Figure 1a shows a typical crystal size distribution observed experimentally. In particular, we refer to the distribution observed for the Run B at time $t = 26.5 \text{ min}$. The crystal size distribution shows a bimodal shape: at high sizes the distribution of the crystals follows a symmetric bell shaped curve when analyzed in the logarithmic scale, whereas a significant tail is observed at lower sizes. The presence of a low size tail is mainly due to secondary

nucleation phenomena that lead to a not negligible ratio of crystals still nucleating even after the principal nucleation has taken place. This aspect is more evident in Figure 1b where the corresponding cumulative distribution function (CDF) is reported in the normal probability scale (solid line). One should remind that, if the CDF was normal, this kind of plot would appear as linear, whereas other distribution types will introduce some curvature. For the present case, a significant deviation from the ideal linear case is observed only in the region of very small crystals. Thus one can conclude that the basic shape of the particle size distribution reminds a log-normal one. This scenario is compatible with a decaying nucleation rate accompanied by a surface controlled growth (Kile et al., 2005), and confirms that the GBM assumption is a reasonable choice for the present experimental scenario.

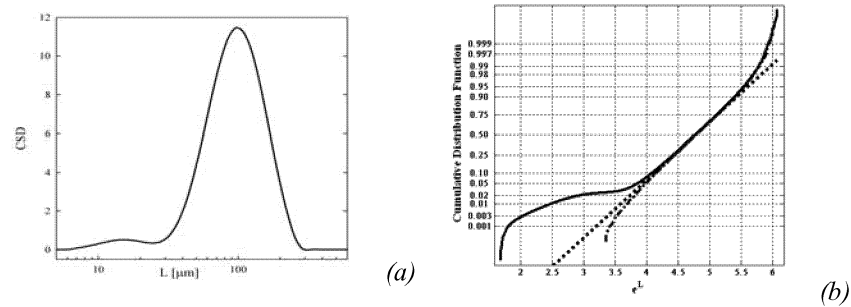


Figure 1: (a): particle size distribution at time $t = 26.5$ min (Run B); (b) experimental Cumulative Particle Size Distribution vs the crystal size (logarithmic scale), the corresponding adjusted Cumulative Distribution obtained by removing the low crystal size tail (dashed line), ideal Gaussian distribution is represented by the dotted line.

Tails at low size values come from secondary nucleation, whose mechanism is not described by the current model. Therefore, the experimental PDF will be filtered by removing the points at low size values, with a shape-preserving piecewise cubic interpolation. For sake of completeness, the adjusted Cumulative Distribution obtained by removing the low crystal size tail (dashed line), is also reported in the figure 1B, where it is possible noticing a qualitative agreement with the Gaussian ideal case.

4. Results and Discussion

The parameters, θ of the model (i.e. the velocity growth rate, r , the saturation value K and the diffusion D) are assumed to depend on the feeding rate condition V_0 . As a consequence the model calibration is carried out separately for every run. Eventually, the parameters to be estimated are: $\theta = [\log(D), r, K]$ (parameter $\log(D)$ was used instead of D in order to reduce the statistic correlation between the parameters). It should be noted that direct measurements of the Particle Size Distribution are available at N different spatial locations and at M different time values for every operating condition, i.e. anti-solvent flow rate. The parameters θ are estimated by using the least square criterion, thus searching the minimum of the objective function:

$$\Phi(\theta) = \Phi(r, K, D) = \sum_{j=1}^M \sum_{k=1}^N (\psi_{\text{mod}}(y_k, t_j; \theta) - \psi_{\text{exp}}(y_k, t_j))^2 \quad (7)$$

In Equation 7, $\psi_{\text{mod}}(y_k, t_j)$ is the probability density function evaluated through numerical integration of Equation 5, at time t_j and size coordinate y_k , while the distribution $\psi_{\text{exp}}(y_k, t_j)$ is the experimental observation of the PSD for the size coordinate y_k at time t_j . The model calibration is thus carried out by comparing N point observations of the distribution ($N \sim 40$), monitored at M different times (M between 6 and 10, depending on the experimental run). The minimum search is carried out by the Levenberg-Marquardt method. As it regards the supplementary run at intermediate feeding rate, this was used for an *a-posteriori* model validation. The parameter estimation values together with an estimation of the mean square error (*MSE*) are given in Table 1 for the experimental runs. For sake of completeness the M value for every run is also reported.

Table 1: Point estimation of the parameters for the three runs

	M	$\log(D)$	r	K	MSE
Run A	10	-2.402	1.788e-2	4.8779	7.96e-4
Run B	7	-2.391	1.800e-2	4.8640	2.84e-4
Run C	6	-1.702	8.475e-2	4.6781	4.09e-4

The Mean Square Error is rather small, thus revealing a good agreement between experimental points and model predictions. The comparison is also carried out by reporting the time evolution of the first moment of the distribution, i.e., the mean, μ

$$\mu(t) = \int_{\Omega} L \psi(L, t) dL$$

Figure 2 shows the first moment experimentally observed (square points) compared with the theoretical predictions (solid line) for the three runs as a function of time. The agreement is rather good at each time and the FPE model, driven by its deterministic part (the logistic growth term), correctly describes the increasing trend of the average crystal growth. In Figure 2b we also report experimental data provided by the second experimental run (cross points), (not used for the parameter inference), demonstrating that the model has good predictive capabilities.

5. Conclusion

A stochastic phenomenological model for the description of antisolvent crystal growth processes is here proposed. The crystal size is considered as a random variable, whose probability density evolution in time is described in terms of a Fokker-Planck equation. The model is tested on data provided in a bench-scale fed-batch crystallization unit where anti-solvent is added to speed-up the crystal formation process. The FPE formulation appears as a powerful predictive tool, as confirmed by the excellent agreement with the experiments.

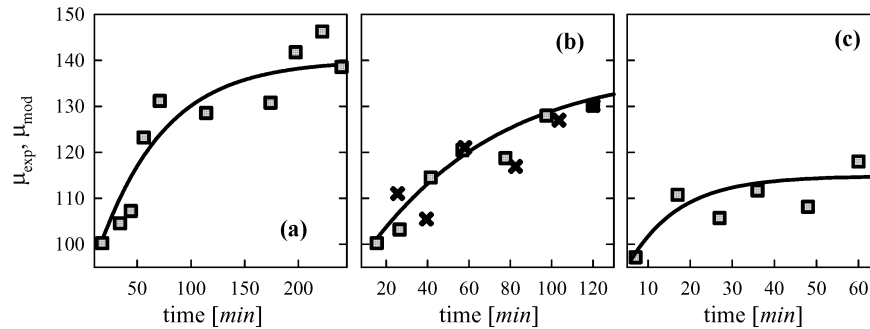


Figure 2: Mean of the Crystal Size Distributions vs time for the different feeding rates.

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