

A Stochastic Formulation for the Prediction of PSD in Crystallization Processes: Comparative Assessment of Alternative Model Formulations

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Abstract: A stochastic formulation for the description of antisolvent mediated crystal growth processes is discussed. In the proposed approach the crystal size growth dynamics is driven by a deterministic growth factor coupled to a stochastic component. The evolution in time of the particle size distribution is then described in terms of a Fokker-Planck equation. In this formulation the specific form of the stochastic model leads to different shapes for the probability density function. In this work we investigate and assess comparatively the performance of the FPE approach to model the crystal size distribution based on different expressions for the stochastic component. In particular, we consider the Langevin equation with a multiplicative noise term that depends on the crystal size (time and space). It is shown and corroborated via experimentation that the best stochastic model is given by the Geometric Brownian Motion (GBM). Excellent quantitative agreement between experiments and the predictions from the FPE-GBM model were obtained for a range of conditions. Validations against experimental data are presented for the NaCl-water-ethanol anti-solvent crystallization system.

Keywords: particle size measurement, Brownian motion, process parameter estimation, probabilistic models, stochastic modeling.

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; Nagy et al., 2008).

An alternative approach to deal with particulate systems characterized by PSD is the Fokker-Planck Equation (FPE) (Risken, 1984; Grosso et al., 2009). 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.

This work describes a novel stochastic approach for the prediction of the PSD 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). Unknown dynamics, internal and external fluctuations and sensitivity to initial conditions can be taken into account by embedding the logistic equation into the FPE (Grosso et al. 2009).

However, in the FPE formulation the specific form of the stochastic model leads to different shapes for the predicted probability density function. In this work we investigate and assess comparatively the performance of the FPE approach to model the crystal size distribution based on different expressions for the stochastic model. In particular, we consider the Langevin equation with a multiplicative noise term that may or not depend on the crystal size (time and space). We show that for a special form of the multiplicative noise term we can actually shape the probability density function of the crystal growth process to adequately represent the experimental information. Validations against experimental data are presented for the NaCl-water-ethanol anti-solvent crystallization system. Experimental data for

different operating conditions are used for parameter estimation and model validation.

2. PSD ESTIMATION

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 on 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:

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

In Equation 1, $f(L, \theta, t)$ 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, $g(L)\eta(t)$ is the multiplicative noise term where $g(L)$ is the diffusion term and $\eta(t)$ is the Langevin force. It is assumed that:

$$\begin{aligned} E[\eta(t)] &= 0 \\ E[\eta(t)\eta(t')] &= 2\sqrt{g(L)}\delta(t-t') \end{aligned} \quad (2)$$

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 . Incidentally, it should be noted that one can regard the probability density $\psi(L, t)$ 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, $\psi(L, t)$, at any instant of time t and should follow the linear Fokker-Planck Equation, FPE:

$$\begin{aligned} \frac{\partial \Psi(L, t)}{\partial t} = \\ \frac{\partial}{\partial L} (g(L)) \frac{\partial}{\partial L} [g(L)\Psi(L, t)] - \frac{\partial}{\partial L} \Psi(L, t) L f(L, t, \theta) \end{aligned} \quad (3)$$

along with the boundary conditions:

$$f(0)\Psi(0, t) - g(L) \frac{\partial}{\partial L} \Psi(0, t) = 0 \quad (4a)$$

$$\frac{\partial}{\partial L} \Psi(\infty, t) = 0 \quad (4b)$$

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 $\psi(L, t)$ as L goes to infinity, for any time.

The diffusion term $g(L)$ determines the random motion of the variable L that takes into account the fluctuation in the particle growth process. The well established property of the normal diffusion described by the Gaussian distribution can be obtained by the usual FPE with constant diffusion term (without a drift term). Anomalous diffusion regimes can also be obtained by the usual FPE but they arise from a variable diffusion term that depends on time and/or space (Fa, 2005). Along the same idea, in our formulation the specific form of $g(L)$ leads to different shapes for the probability density function. In this work we investigate and assess comparatively the performance of the FPE approach to model the crystal size distribution based on different expressions for $g(L)$. In this regard we focus on three possible formulations for $g(L)$ as discussed below.

Case 1: As first option a constant value of $g(L) = 2\sqrt{D}$ can be assumed, where D is the typical diffusivity coefficient in the FPE formulation. In this case

$$\frac{dL}{dt} = Lf(L; \theta, t) + 2\sqrt{D}\eta(t) \quad (5)$$

We should notice that: i) when the deterministic drift term is $f=0$, equation 5 describes the classical Wiener process; ii) when f depends linearly on L , Equation (5) describes an Ornstein-Uhlenbeck process. In both cases the random variable L will follow a Gaussian distribution. Equation 5 can

be manipulated to obtain the Langevin equation for the random variable $y = \ln L$.

$$\frac{1}{L} \frac{dL}{dt} = f(L; \boldsymbol{\theta}, t) + 2\sqrt{D} \frac{1}{L} \eta(t) \quad (6)$$

that is

$$\frac{dy}{dt} = h(y; \boldsymbol{\theta}, t) + 2\sqrt{D} e^{-2y} \eta(t) \quad (7)$$

The FPE for the new random variable y can be rewritten as

$$\frac{\partial \Psi(y, t)}{\partial t} = D \cdot e^{-2y} \left(\frac{\partial^2 \Psi}{\partial y^2} - 3 \frac{\partial \Psi}{\partial y} + 2\Psi \right) - \frac{\partial}{\partial y} \Psi(y, t) h(y, t, \boldsymbol{\theta}) \quad (8)$$

Case 2: Assuming a linear dependency on the crystal size L , $g(L) = 2L\sqrt{D}$, in this case

$$\frac{dL}{dt} = Lf(L; \boldsymbol{\theta}, t) + 2\sqrt{D} L \eta(t) \quad (9)$$

When f is constant, equation 9 describes a Geometric Brownian Motion (GBM). In this case, the associated PDF is a lognormal distribution (Ross, 2003), If f depends also on L , some (slight) distortions from the ideal lognormal case can be however expected.

Accordingly, equation 9 can be manipulated to obtain the Langevin equation for the random variable $y = \ln L$

$$\frac{dy}{dt} = h(y; \boldsymbol{\theta}, t) + 2\sqrt{D} \eta(t) \quad (10)$$

And the corresponding FPE becomes

$$\frac{\partial \psi(y, t)}{\partial t} = D \frac{\partial^2 \psi}{\partial y^2} - \frac{\partial}{\partial y} \psi(y, t) h(y, t, \boldsymbol{\theta}) \quad (11)$$

Case 3: Assuming an intermediate case where $g(L) = 2\sqrt{L}\sqrt{D}$

In this case

$$\frac{dy}{dt} = h(y; \boldsymbol{\theta}, t) + 2\sqrt{D} e^{-\frac{y}{2}} \eta(t) \quad (12)$$

And the corresponding FPE becomes

$$\frac{\partial \psi(y, t)}{\partial t} = D e^{-y} \left(\frac{\partial^2 \psi}{\partial y^2} - \frac{3}{2} \frac{\partial \psi}{\partial y} + \frac{1}{2} \psi \right) - \frac{\partial}{\partial y} \psi(y, t) h(y, t, \boldsymbol{\theta}) \quad (13)$$

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 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:

$$h(y; \boldsymbol{\theta}, t) = r y \left(1 - \frac{y}{K} \right) \quad (14)$$

This choice is mainly motivated by the requirement for a simple model with a parsimonious number of adjustable parameters, i.e. the growth rate, r , and the asymptotic

equilibrium value K . The present growth model can be regarded as the simplest model taking into account mild nonlinearities. In spite of its 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. 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

For parameter estimation and model validation purposes, three different anti-solvent flow-rates were implemented. All experiments were carried out in a bench scale crystallizer which was kept at a fix temperature. Only purified water, reagent grade sodium chloride (99.5%) and ethanol (95%) 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 computer control system 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 recorded. The crystal size distribution is determined by visual inspection of images taken using a digital camera mounted in a stereo-microscope at 25× magnification. 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 vacuum filtered over filter paper and then dried in an oven at 50 °C for further visual inspection. Figures 1 and 2 illustrate the images obtained at the first sampling time and at the end of the experiment sampling time for the medium antisolvent flow-rate of 1.5 ml/min

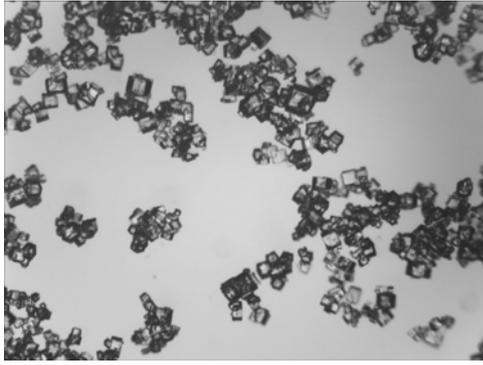


Figure 1: Feed rate 1.5 ml/min. NaCl crystals at $t = 0.5 h$

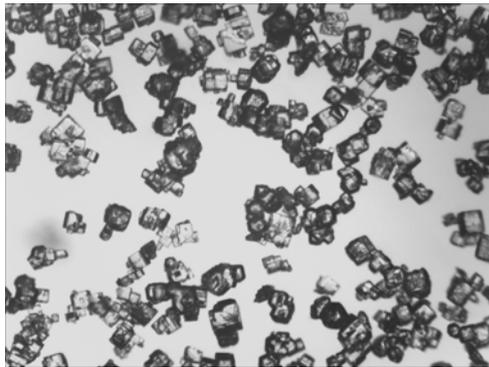


Figure 2: Feed rate 1.5 ml/min. NaCl crystals at $t = 8 h$

The captured images, for each sampling point during batch run, are then processed by means of the sizing computer software (Amscope®) to obtain the particle size distribution (see histogram in Figure 3).

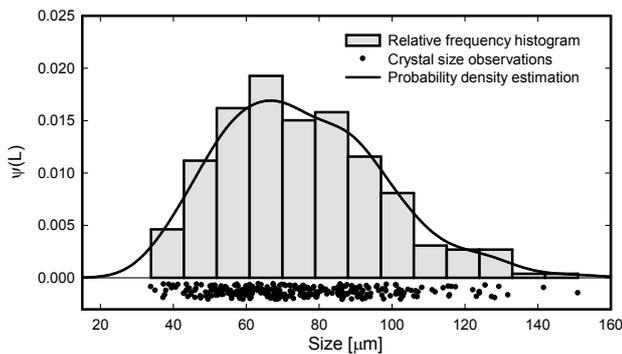


Figure 3: Relative frequency density of the crystal sample at feed rate $u_0 = 1.5 \text{ ml/min}$ and $t = 0.5 h$ (bars), compared with the kernel approximation (solid line). The n observations of the sample are also reported at the bottom of the figure (black points)

3.3 Characterization of the experimental PSD

The crystal size sample is further processed in order to infer the related probability density function. To this end, a non-parametric method was used and the experimental probability density distribution was eventually estimated as a linear combination of kernel basis function:

$$\psi(L) = \frac{1}{nh} \sum_{i=1}^n \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{(L-L_i)^2}{2h^2}\right) \quad (15)$$

where n is the crystal sample dimension, L_i is the i -th observation and the bandwidth parameter h is given by (Silverman, 1986):

$$h = 1.06\sqrt{s_L^2 n^{-0.2}} \quad (16)$$

In Equation (16), s_L^2 is the sample variance. An example of the distribution estimation obtained with the crystal sample is reported in Figure 3.

Figures 4 and 5 illustrate the experimental PSD evolution (obtained using the kernel density estimation) with time for the intermediate feed rate (1.5 ml/min) both in the linear and logarithmic scale.

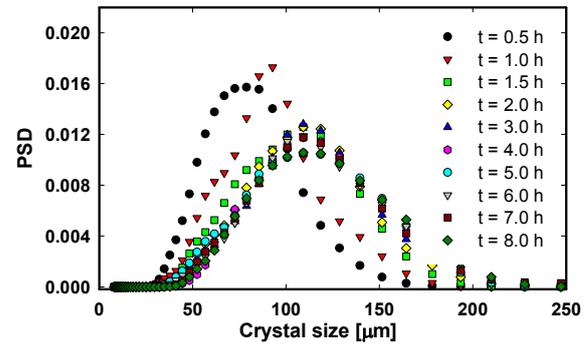


Figure 4: Obtained PSD from experimental data for intermediate antisolvent feed rate of 1.5 ml/min at different sampling times during the batch (linear scale)

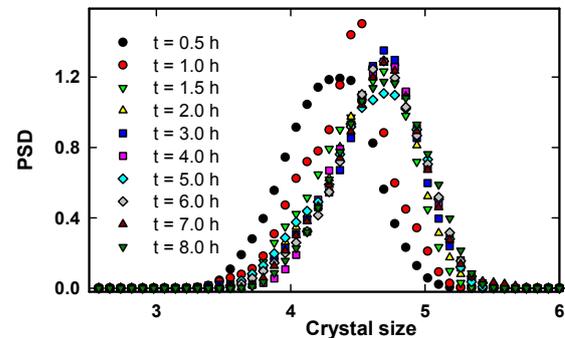


Figure 5: Obtained PSD from experimental data for intermediate antisolvent feed rate of 1.5 ml/min at different sampling times during the batch (logarithmic scale)

4. RESULTS AND DISCUSSION

4.1 Parameter Estimation

Model calibration for the estimation of parameters is carried out separately for every run. The parameters to be estimated are: $\Theta = [\log(D), r, K]$ ($\log(D)$ is 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. Parameter inference is accomplished by using the least square criterion, thus searching the minimum of the objective function:

$$\Phi(\theta) = \Phi(r, K, D) = \sum_{j=1}^M \sum_{k=1}^N (\psi_{\text{mod}}(y_k, t_j; \theta) - \psi_{\text{exp}}(y_k, t_j))^2 \quad (15)$$

In Equation 15, $\psi_{\text{mod}}(y_k, t_j)$ is the probability density function evaluated through numerical integration of Equations 8, 11 and 13 (corresponding to the appropriate model selected, 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 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 $\theta = [r, K, D]$ is estimated using a nonlinear least-square algorithm. The values for the estimated parameters are given in the Table 1.

	Feed Flow	r	K	$\log D$
Case 1 $g(L) = 2\sqrt{D}$	0.7	0.0746	7.200	1.169
	1.5	0.0356	7.993	1.134
	3.0	0.0642	8.530	1.328
Case 2 $g(L) = 2\sqrt{DL}$	0.7	1.254	4.840	0.952
	1.5	1.038	4.691	1.025
	3.0	1.241	4.661	1.026
Case 3 $g(L) = 2\sqrt{D}\sqrt{L}$	0.7	0.914	4.863	0.952
	1.5	1.038	4.691	1.025
	3.0	1.116	4.672	0.981

Table 1: Estimated parameters for the different operating conditions for the three models investigated

4.2 Model Comparisons and Validation

Figure 6 illustrates (in the logarithmic scale) the comparison between the predicted particle size distribution using the three alternative models for the end the batch and for intermediate antisolvent flowrate of 1.5 ml/min. Figure 7 illustrates the same conditions but in the linear scale.

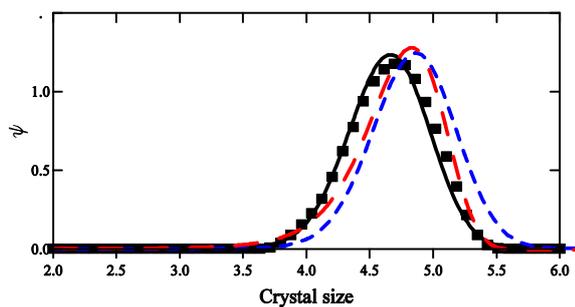


Figure 6: Comparison between model predictions and experimental probability density functions for intermediate feeding rate of 1.5 ml/min (logarithmic scale)

It is clear from the figures that the use of the GBM as stochastic component is more appropriate to describe the PSD of the crystallization process.

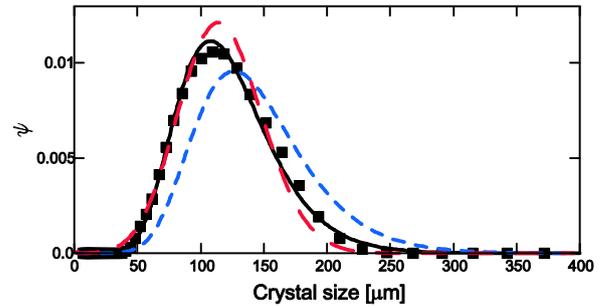


Figure 7: Comparison between model predictions and experimental probability density functions for intermediate feeding rate of 1.5 ml/min (linear scale)

The differences on the predictive features of the models are even more evident in the normal scale. More insight into the descriptive characteristics of the alternative models can be obtained by analyzing the time evolution of the experimental observations and the corresponding model prediction for first moments of the distribution, i.e., the mean, μ and the variance σ^2 :

$$\mu(t) = \int_{\Omega} (L \Psi(L, t) dL ; \sigma^2(t) = \int_{\Omega} (L - \mu(t))^2 \Psi(L, t) dL \quad (16)$$

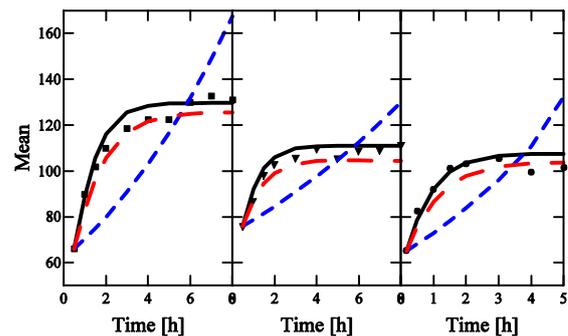


Figure 8: Mean of the Crystal Size Distributions for the three feeding rates and three different models. Square points are the experimental observation.

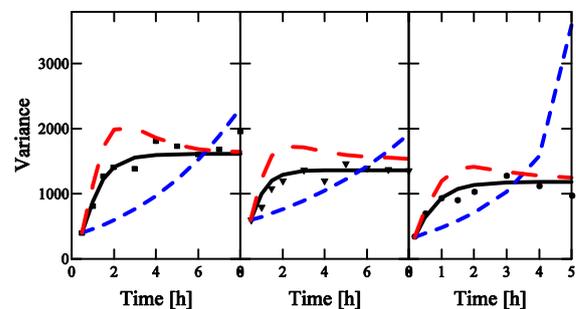


Figure 9: Variance of the Crystal Size Distributions for the three feeding rates and three different models. Square points are the experimental observation.

Figures 8 and 9 show, respectively, the mean and variance experimentally observed (squared points) compared with the theoretical predictions (solid line $g(L) = 2L\sqrt{D}$; dashed line

$g(L)=2\sqrt{L}\sqrt{D}$ and dotted line $g(L)=2\sqrt{D}$) for the three runs and for the three models as a function of time. The agreement again is excellent at each time using the GBM stochastic component and the FPE model, driven by its deterministic part (the logistic growth term), correctly describes the increasing trend of the average crystal growth. On the other hand, the performance of the model deteriorates when using the alternative models both in terms of the mean and variance predictions.

Finally, Figure 10 reports the comparison (in terms of time evolution) of the PSD experimentally observed and the model prediction (using the FPE-GBM model) for the experiment at low, medium and high feed rates, at the first and final acquisition time. It is evident that there is an excellent quantitative agreement between experiments and the predictions from the phenomenological model. In particular, the model is able to correctly capture the log-normal shape of the experimental PSD as well as follow the dynamic of the crystal growth for a range of operating conditions.

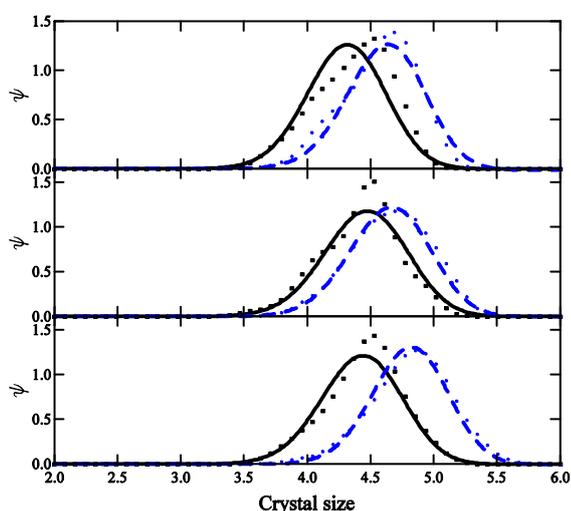


Figure 10: Comparison between model and the experimental probability density functions for the three feeding rates and at the first sampling time and at the end of the batch sampling time.

5. CONCLUSIONS

A stochastic formulation for the prediction of the antisolvent crystal growth processes has been discussed. The crystal size is considered as a random variable, whose probability density evolution in time is described in terms of a Fokker-Planck equation. In the proposed formulation the specific form of the stochastic model chosen leads to different shapes for the probability density function. We have investigated and assessed comparatively the performance of the FPE approach to model the crystal size distribution based on different expressions for the stochastic component. It is shown and corroborated via experimentation that the best stochastic model is given by the Geometric Brownian Motion (GBM). Excellent quantitative agreement between experiments and the predictions from the FPE-GBM model were obtained for a range of conditions. In particular, the model was able to correctly capture the log-normal shape of the experimental PSD. The model was 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-GBM formulation appears as a powerful predictive tool, as confirmed by the excellent agreement with the experiments, to represent the anti-solvent crystal growth process.

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