

## Stochastic Global Model for the Prediction of the Asymptotic CSDs Using Antisolvent Crystallization Processes

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A stochastic global formulation describing antisolvent mediated crystal growth processes based on the Fokker-Planck equation (FPE) is discussed. The obtained global model is used to define an operating map of the crystallization process, where asymptotic iso-mean and iso-variance curves are reported in an antisolvent flow rate – temperature plane. The asymptotic solutions of the obtained global model evidenced the occurrence of input multiplicities for a certain window of operating conditions. This implies that it is possible to obtain the same asymptotic Crystal Size Distribution (CSD) by using two different sets of input values. This particular behavior has been corroborated experimentally and it is due to the presence of competing effects of the process inputs. Using the obtained asymptotic operational map, three different CSDs have been predicted and compared, both in asymptotic and then in dynamic conditions, using experimental results.

### 1. Introduction

Crystallization is a critical part of processing in fine chemicals and pharmaceutical industries where crystal size can largely influence the textural and physical properties of the final commercial products. Several factors can affect the size and the widening of the size distribution, therefore its control is an important and challenging problem.

The development of effective mathematical models describing the crystal growth dynamics is a crucial issue toward finding the optimal process performance and to control the characteristics of the product. Antisolvent crystallization has been modeled for many systems using the traditional population balance modeling method (Woo et al., 2006; Zhou et al., 2006; Nowee et al., 2008a/b; Sheikhzadeh et al., 2008; Trifkovic et al., 2008). In this approach, the number of crystals in a semi-batch crystallizer increases by nucleation and decreases by dissolution or breakage, and the crystals are classified by their size. The population balance provides more detailed information regarding the crystal size distribution in the crystallization unit, but it requires a great deal of knowledge on the thermodynamic properties associated with the solute and solvent to be incorporated into the structured population balances.

An alternative and novel approach to deal with particulate systems characterized by crystal size distribution (CSD) has been proposed and implemented recently and it is based on modeling the growth process in terms of a Fokker-Planck Equation (Grosso et al., 2009; Galan et al., 2010; Grosso et al., 2010a-b; Grosso et al., 2011). In this approach, the fluctuations of the particle state, due to different uncertainty sources (e.g., turbulence at micro-scale mixing, temperature fluctuations, etc.) during the crystallization, can be modelled as a random self-organizing and complex process. The Fokker-Planck equation (FPE) is used in the approach in order to explain the observed macroscopic behaviour of crystal growth in antisolvent aided crystallization. Models based on Fokker-Planck equations have been used in different science, such as atmospheric sciences, financial market

dynamics, polymerization (Egger, 1981; Vallis, 1988; Michael, and Johnson, 2003; Hosseini et al., 2013) among others.

Within the antisolvent crystallization process, the Fokker-Planck approach gives a novel description, in a compact form, of the crystal size distribution dynamics and leads to the obtainment of a simpler model with the possibility to have analytical solution for describing the CSD over time (Tronci et al., 2011; Cogoni et al., 2012).

The proposed Fokker-Planck-based model, however, does not have an explicit dependency of the control inputs (i.e., antisolvent flow rate and temperature), although the model parameters are affected by operating conditions. In the previous works, the stochastic model has been used when varying antisolvent flow rate values, exploiting a linear piece-wise interpolation approach (Grosso et al., 2010a; Tronci et al., 2011). Even though effective results were obtained with this procedure, the use of linear interpolation does not lead to the obtainment of a continuous input-output relationship, as in case of model-based control algorithms. Furthermore, considering the effect of other input variables, as for example the system temperature, makes the piece-wise interpolation procedure more complex also because the number of parameters to be estimated for covering the operability region increases.

A solution for the obtainment of a global stochastic model is here proposed, where an explicit relationships between FPE parameters and process variables has been developed. The model is then used to define the feasible output region in terms of mean crystal size and variance, which means defining an operating map where the first two moments of the CSD, at asymptotic conditions, are reported in a temperature-flow rate plane. This representation is a useful tool to support process conduction in terms of selection of input trajectories, which minimizes antisolvent and energy consumption. Results are provided through investigations in the nonisothermal antisolvent crystallization of sodium chloride (NaCl), which solubility is practically independent of temperature.

## 2. Experimental work

The experiments were performed in a bench scale crystallizer, where only purified water, reagent grade sodium chloride (99.5 %) and ethanol, 190 proof, were used. The experimental rig is comprised of a 1 liter jacketed reactor connected to a Thermo Scientific® cooling/heating bath circulator that provides to keep constant the temperature inside the reactor by an embedded PID controller and a thermocouple wired inside the reactor. The antisolvent is added using a Masterflex® peristaltic pump calibrated for each experiment.

At the start-up condition of the experimental run, the crystallizer is loaded with an aqueous solution of NaCl made up of 34 g of NaCl dissolved in 100 g of water. The experiments are then conducted at constant operating conditions, considering three different values for the temperature (10 °C, 20 °C, 30 °C) and four values of antisolvent flow rate (0.7 ml/min, 1.5 ml/min, 2.25 ml/min, 3.0 ml/min), therefore the experimental campaign consisted of twelve runs (full factorial design), nine of them using to calibrate the model and three used for validation. Along the operation, 8 ml samples were taken in an infrequent fashion. Samples were then vacuum-filtered over filter paper and then dried in an oven, at least for 24 h, with a constant temperature of 50 °C for further visual inspection (Grosso et. al., 2010a).

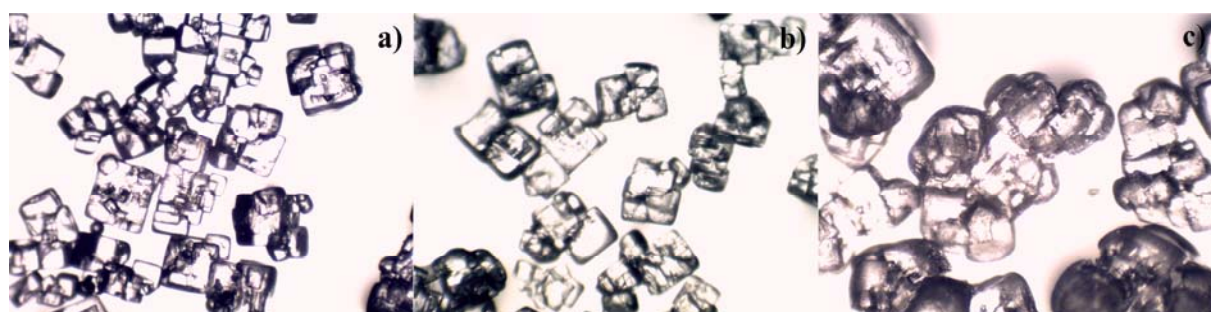


Figure 1: Typical images taken during the experimental runs

Crystal size measurement has been accomplished by means of a light microscopy. A stereo light microscope (Wild-Heerbrugg, Switzerland) was used and connected to a digital camera (Amscope Model MD500, United States). Several images were taken with the camera for each sample and analyzed using the AmScope software (iScope, United States). The software allows for the measurement of the length or area of particular crystals in units of pixels. Using a supplied calibration slide, these lengths and areas can be converted to a micron length

scale. The number of crystals measured varied for each sample and was fixed by a stabilization criterion of  $\pm 2.5\%$  of the mean. Figure 1 illustrates typical parts of the images obtained during the experiment sampling time.

### 3. Stochastic modelling approach

A stochastic formulation to describe the time evolution of the particle size distribution in an anti-solvent crystallization process was recently introduced (Grosso et al. 2010a; Galan et al. 2010). In this approach, the crystals are classified by their size,  $L$ . The growth of each individual crystal is supposed to be independent by the other crystals and it is assumed to be governed by a deterministic and a stochastic term:

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

In Eq. (1)  $g(L; \theta)$  represents the deterministic contribution to the growth rate of  $L$ , defined as a Gompertz model (Cogoni et al., 2012),  $\theta$  is the vector parameter defined in the model,  $L\eta(t)$  is the a random component linearly depending on crystal size, and  $\eta(t)$  is the Langevin force. It is further assumed that:

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

where  $\Lambda$  is the intensity of the Langevin force, which has been assumed as constant and equal to  $\sqrt{D}$ , and  $D$  is the diffusivity parameter of the FPE. Equations (1) and (2) imply that the crystal size  $L$  behaves as a random variable, characterized by a certain Probability Density Function (PDF) depending on the state variables of the system, i.e. the size  $L$  and time  $t$

Equation (1) can be manipulated to obtain the Langevin equation for the new random variable  $y = \ln L$  (Grosso et al., 2010a):

$$\frac{dy}{dt} = r\left(1 - \frac{y}{K}\right) + \eta(t) \quad (3)$$

The PDF related to the  $y$  random variable can then be described by the following linear Fokker-Planck equation with linear coefficients:

$$\frac{\partial \psi(y, t)}{\partial t} = D \frac{\partial^2 \psi(y, t)}{\partial y^2} - \frac{\partial}{\partial y} \left[ r\left(1 - \frac{y}{K}\right) \psi(y, t) \right] \quad t \geq 0, y \in \mathfrak{R} \quad (4)$$

The initial condition for  $t = t_0$  is assumed as a normal distribution:

$$\psi(y, t_0) = \frac{1}{\sigma_0 \sqrt{2\pi}} \exp\left[-\frac{(y - \mu_0)^2}{2\sigma_0^2}\right] \quad (5)$$

where  $\mu_0$  and  $\sigma_0$  are, respectively, the initial mean size of crystals (logarithmic scale) and the initial standard deviation at  $t = t_0$ .

Being the coefficient of Equation (4) linearly dependent on  $y$ , the distribution  $\psi(y, t)$  preserves the Gaussian shape at any time (Cogoni et al., 2012), thus the PDF can be easily described by its first two moments, the mean,  $\mu(t)$ , and the variance,  $\sigma^2(t)$ :

$$\psi(y, t) = N(\mu(t), \sigma^2(t)) \quad (6)$$

Respectively given by:

$$\mu(t) = K \left[ 1 - \left( 1 - \frac{\mu_0}{K} \right) e^{-\frac{r}{K}(t-t_0)} \right] \quad (7)$$

$$\sigma^2(t) = \sigma_0^2 e^{-2\frac{r}{K}(t-t_0)} + \frac{DK}{r} \left[ 1 - e^{-2\frac{r}{K}(t-t_0)} \right] \quad (8)$$

The asymptotic conditions in terms of mean and variance is given by the following relationships:

$$\mu_{SS} = K \quad (9)$$

$$\sigma_{SS}^2 = \frac{DK}{r} \quad (10)$$

As further step, it is necessary to transform the solution from logarithmic to linear scale, and the following expressions have been used:

$$\mu_{Lin}(t) = \exp\left(\mu_{ln}(t) + \frac{\sigma_{ln}^2(t)}{2}\right) \quad (11)$$

$$\sigma_{Lin}^2(t) = [\exp(\sigma_{ln}^2(t)) - 1] \exp(2\mu_{ln}(t) + \sigma_{ln}^2(t)) \quad (12)$$

#### 4. Stochastic global model

Parameters estimation for the Fokker-Planck based model describing the crystal growth has been first carried out separately for every operating condition, using the experimental data obtained at three different values of temperature ( $T=10^\circ\text{C}$ ,  $20^\circ\text{C}$ ,  $30^\circ\text{C}$ ) and three different values of antisolvent flow rate ( $q=0.7$  ml/min,  $1.5$  ml/min,  $3.0$  ml/min). The parameters have been obtained by applying the maximum likelihood estimation approach (Equation 13):

$$\ln L(\theta | y_m) = \ln \prod_{m=1}^{n_e} \psi(y_m(t_{j,k}), \theta) = \sum_{k=1}^{n_e} \sum_{j=1}^{n_k} \sum_{l=1}^{n_{j,k}} \ln \psi(y_{l,k}(t_{j,k})) \quad (13)$$

$$n_t = \sum_{k=1}^{n_e} \sum_{j=1}^{n_k} n_{j,k}, \quad \theta = (r, K, D)$$

where  $\theta$  is the vector of parameters,  $y_m$  is the value in logarithmic scale of the  $m$ -th experimental observation for the crystal size ( $m = 1, \dots, n_e$ ),  $n_e$  is the number of experimental runs carried out varying input parameters,  $n_k$  is the number of sampling time,  $n_{j,k}$  is the number of crystal size measurements collected at time  $t_{j,k}$ . It is worth noting that being the coefficient of Equation (4) linearly dependent on  $y$ ,  $\psi(y,t)$  is a Gaussian distribution with mean and variance calculated by means of Equation (7) and (8). The values of the estimated parameters are reported in Table 1, along with the temperature and antisolvent flow rate set for every run.

It is evident from the results in Table 1 that the three parameters are significant affected from the process conditions, and in order to use the proposed crystallization model over the whole operating range, linear piecewise interpolation approaches have been so far exploited (Grosso et al., 2010a; Tronci et al., 2012). Even this approach led to good results, it has the following disadvantages: (i) the model function has discontinuous derivatives with respect to operating conditions (temperature and antisolvent flow-rate), therefore it does not lead to a continuous input-output relationship useful for control purposes, and (ii) it can give an unfair representation when the dependency is far from linearity.

It is possible to obtain a continuous global model finding an explicit dependency of the parameters on input variables, in the understanding that a simple and parsimonious model needs to be found for describing the variations of  $r$ ,  $K$ , and  $D$  with temperature and antisolvent flow rate. By inspection of Table 1 it is possible to assume that model parameters have linear or weak nonlinear dependence on manipulated variables. For the case at hand, simple linear or quadratic dependences have been preferred to describe the input-parameter

relationships, avoiding the cross term dependence on  $T$  and  $q$ . The best model obtained using the Akaike Index Criterion is reported below:

$$\begin{aligned} r(q, T) &= \gamma_{0r} + \gamma_{1r}q + \gamma_{2r}T \\ K(q, T) &= \gamma_{0K} + \gamma_{1K}q^2 + \gamma_{2K}T^2 \\ D(q, T) &= \gamma_{0D} + \gamma_{1D}q^2 + \gamma_{2D}T \end{aligned} \tag{14}$$

Table 1: Model parameters calculated at different operating conditions for the stochastic model

<b>R</b>	<b>10 °C</b>	<b>20 °C</b>	<b>30 °C</b>
<b>0.7 ml/min</b>	1.0646	1.5700	0.7312
<b>1.5 ml/min</b>	1.9343	1.4029	1.1030
<b>3.0 ml/min</b>	3.2860	3.4428	1.9420
<b>K</b>	<b>10 °C</b>	<b>20 °C</b>	<b>30 °C</b>
<b>0.7 ml/min</b>	4.9303	4.9501	5.0713
<b>1.5 ml/min</b>	4.8583	4.9298	5.0489
<b>3.0 ml/min</b>	4.7095	4.7656	4.8659
<b>D</b>	<b>10 °C</b>	<b>20 °C</b>	<b>30 °C</b>
<b>0.7 ml/min</b>	0.1957	0.3992	0.1270
<b>1.5 ml/min</b>	0.3732	0.2163	0.1713
<b>3.0 ml/min</b>	0.7186	0.6735	0.2912

The coefficients of expressions (14) have been estimated using again the Maximum Likelihood Method, for the nine experimental runs, conducted at  $T = (10, 20, 30) ^\circ\text{C}$  and  $q = (0.7, 1.5, 3.0) \text{ ml/min}$ . The coefficients obtained have been reported on Table 2. The following behaviour can be treasured: (i)  $r$  increases with antisolvent flow rate and decreases with temperature; (ii)  $K$  decreases with antisolvent flow rate and increases with temperature and (iii)  $D$  increases with antisolvent flow rate and decreases with temperature (Cogoni et al, 2013). In fact, increasing antisolvent flow rate leads to higher nucleation rates ( $r$  increases), but reduces the average asymptotic crystal size ( $K$  decreases).

Table 2: Values of the model parameters describing the dependence of ( $r$ ,  $K$ ,  $D$ ) on antisolvent flow rate and temperature.

$\gamma_{0r}$	5.7639
$\gamma_{1r}$	2.8342
$\gamma_{2r}$	-0.1584
$\gamma_{0K}$	4.8593
$\gamma_{1K}$	-0.0244
$\gamma_{2K}$	2.0 E-4
$\gamma_{0D}$	0.3864
$\gamma_{1D}$	0.0287
$\gamma_{2D}$	-0.0094

Temperature has an opposite effect as already discussed in the non-isothermal antisolvent crystallization of sodium chloride (NaCl). Higher values of temperature, decreases  $r$  and reduces the driven force for nucleation and favours crystal growth ( $K$  increases). The operating conditions that favour nucleation determine a higher dispersion of the PSD, and this aspect has been correctly reconstructed by the behaviour of coefficient  $D$ .

The mean crystal size calculated with the global model is shown in Figure 2, for the experimental conditions used for parameter estimation. The match between calculated  $\mu_L(t)$  and experimental values is rather good, indicating that Equations (14) correctly approximate the input-parameter relationships.

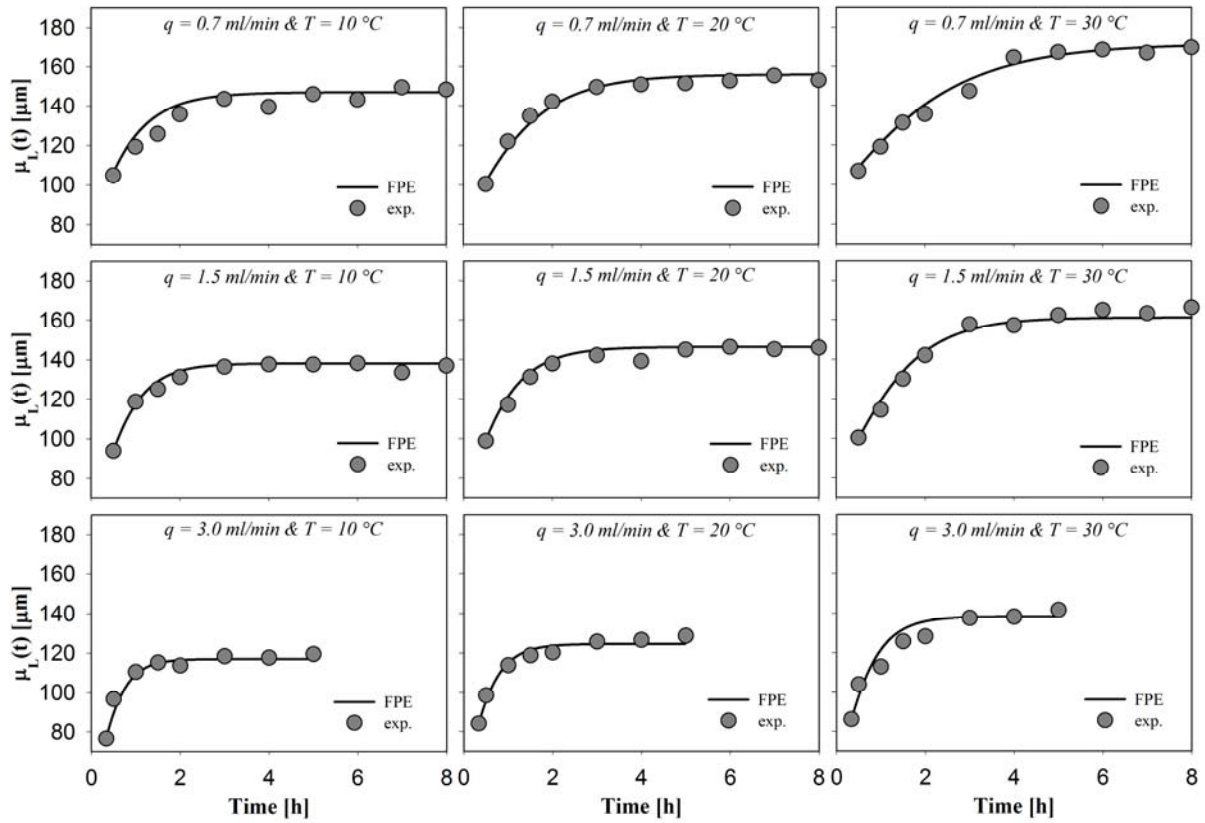


Figure 2: Time evolution of the mean size of crystals (circle) experimental data and (line) predicted.

## 5. Model validation

The ability of the proposed global model to predict the crystal size distribution has been evaluated by comparing calculated values with the experimental data obtained at operating conditions different from the ones used for parameter estimation. In particular, model prediction have been compared with the experimental data obtained carrying on three runs at 10 °C, 20 °C and 30 °C, using a constant antisolvent flow rate, set equal to 2.25 ml/min. The results are reported in Figure 3, where the upper row represents the calculated CSD and the experimental histograms at asymptotic conditions, and the second row shows the time evolution of the predicted and experimental mean crystal size. The fitting is good for all the three situations, indicating that the proposed model is able to give a good description of the crystallization system when changing the operating conditions. It is worth noticing that the relationships used to describe the dependence of the model parameter on the inputs are very simple, with weak nonlinearities, but sufficient to obtain satisfactory representation of the system. The simplicity is an important aspect when a model can be used to develop model-based control system.

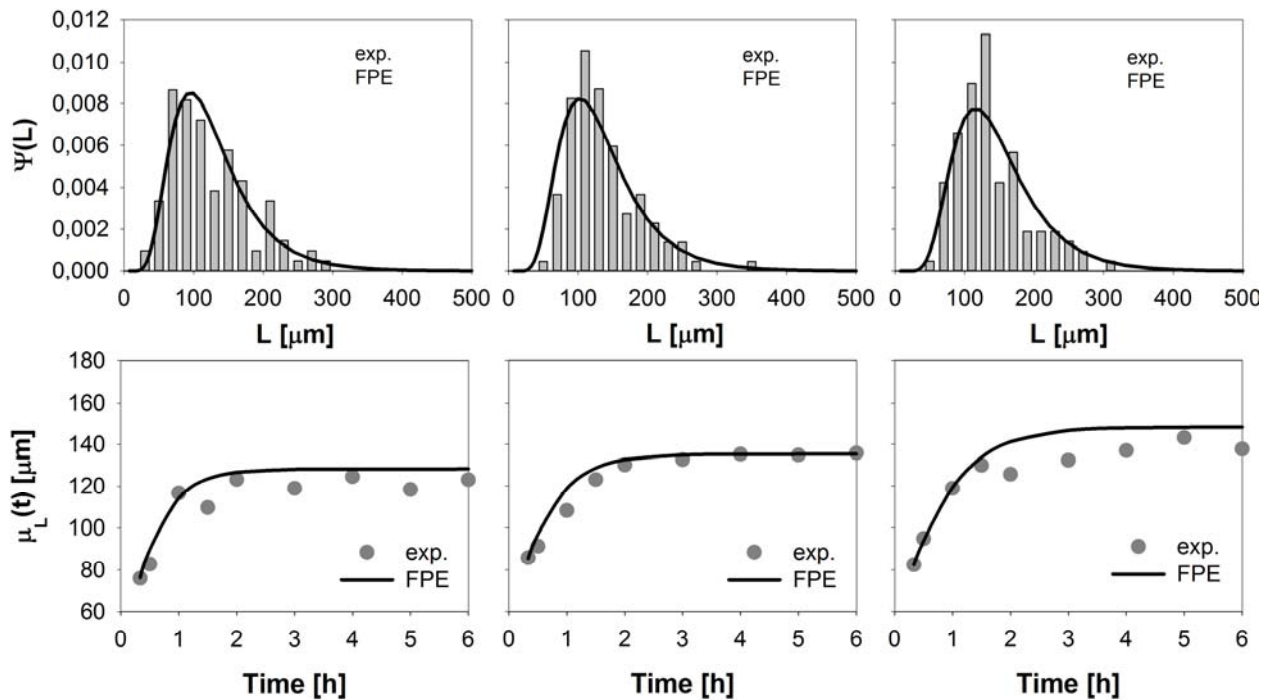


Figure 3: First row: asymptotic CSDs (line) predicted, (histogram) experimental. Second row: time evolution of the mean size of crystals (circle) experimental data and (line) predicted. The results are reported increasing the temperature from the left to the right.

## 6. Operational map

From an operative point of view, the global model can be used to find the inputs values, which drive the system to the desired crystal size distribution, at least in terms of mean crystal size and variance. As a functioning tool for designing the proper crystallization runs, a map can be constructed where asymptotic iso-mean and iso-variance curves are reported in an antisolvent flow rate - temperature plane.

The operational map constructed for the considered system in reported in Figure 4. By inspection of the Figure, it is interesting to note that iso-variance curves may intersect iso-mean curves in two points, therefore the same distribution in terms of the first two moments can be obtained at different operating conditions. In particular, a crystal size distribution with mean equal to 135.4 and variance equal to 3710 (linear scale), can be obtained at  $(q, T) = (2.25, 20)$  and  $(q, T) = (3.0, 30)$ . This result is coherent with the opposite effect that antisolvent flow rate and temperature have on the crystallization process: high asymptotic crystal size can be reached with low  $q$  and high  $T$ , but the same result can be obtained increasing  $q$  and, at the same time, decreasing  $T$ .

In order to better visualize this behaviour, also the results obtained in terms of asymptotic CSDs, for the two set of operating conditions, have been reported (Figure 5). Once again we can affirm that the global model has a good fitting of the experimental data, confirming also the multiplicity of the asymptotic conditions observed in the map.

By inspection of the map in Figure 5 it is also possible to visualize a region at high temperature and high antisolvent flow rate, which have the same asymptotic values of mean and variance reachable at lower conditions. From an economical point of view this region should be avoided, because it requires a higher consumption of antisolvent and of energy for heating the solution. On the other hand, it is important to note that input multiplicities may be difficult to manage when a feedback control is used to track the system along a reference trajectory. This is because the steady-state gains of the system change sign as the system cross frontier line separating the two multiplicity regions.



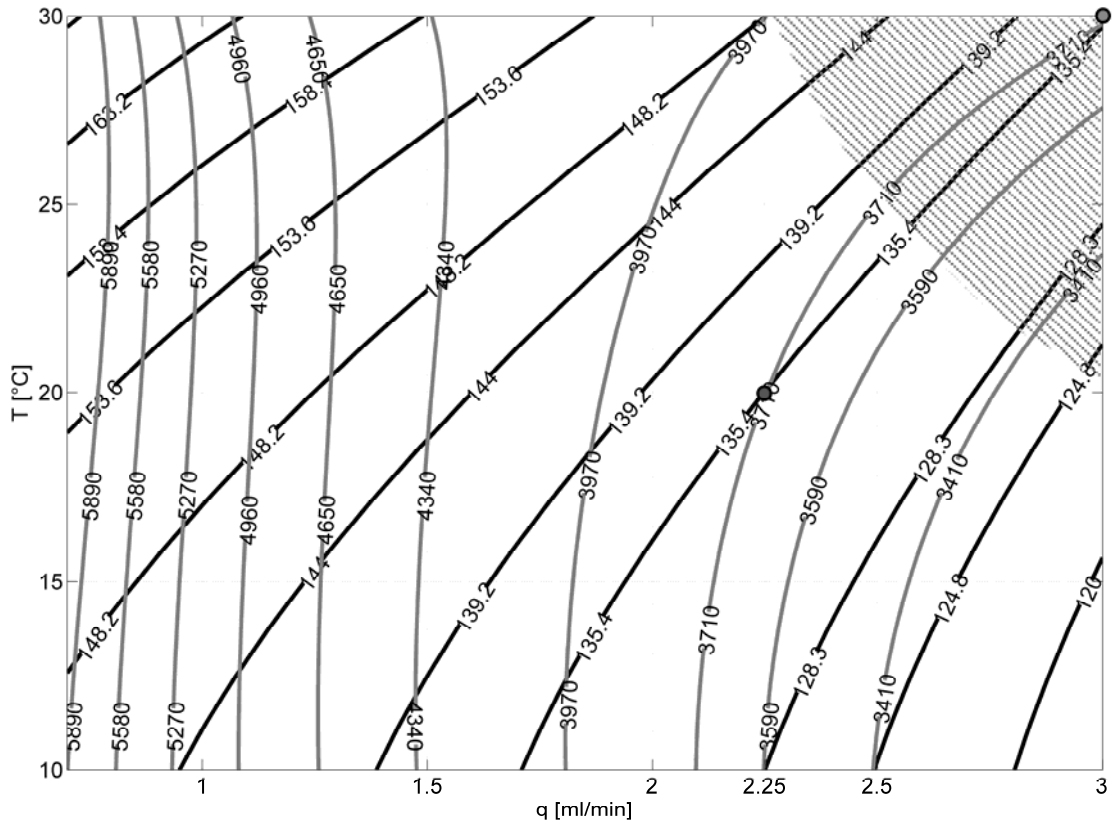


Figure 4: Iso-means - iso-variances map, reported in function of  $T$  and  $q$ , for the linear FPE in linear scale. The black lines represent the means and the grey lines the variances. The two dark grey dots in the map represent a multiple asymptotic CSD. The patterned area represents a region of multiplicity.

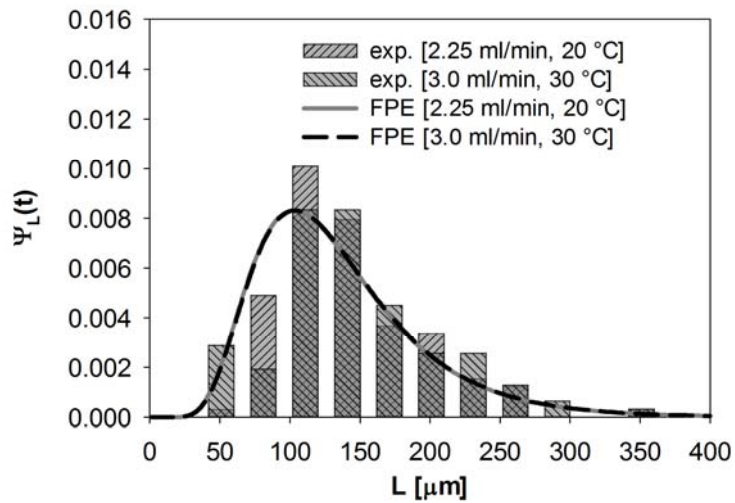


Figure 5: Asymptotic CSDs obtained in the multiple asymptotic CSDs, previously showed in Figure 2, compared to the prediction made with the operating maps.



## 7. Conclusions

The crystallization aided antisolvent process has been here described using the Fokker-Planck approach proposed in previous papers, including the explicit dependency on the manipulated inputs, that are the antisolvent flow rate and temperature. Aiming to the best model description with the minimum mathematical complexity, a global stochastic model has been obtained, characterized by a simple and effective description of the crystallization system with respect to operating conditions. In fact, all the results have been experimentally validated considering the asymptotic CSDs and the dynamic of the mean size of crystals, showing good prediction capabilities.

As first application, the global model has been used to construct an operative map, where the asymptotic values of the first two moments of the predicted CSD (variance and mean size of crystals) has been plotted with respect to the operating conditions (temperature and antisolvent flow rate). From the map it is possible to determine the region of feasibility for specific product characteristics and get the input values necessary to obtain the desired distribution.

As a further and important result, the calculation of the operative map evidenced the occurrence of input multiplicities at asymptotic conditions, also experimentally confirmed. This aspect implies that it is possible to reach the same mean and variance of CSD with two different sets of operating conditions. From an economical point of view, it is therefore convenient to operate at lower antisolvent flow rate and temperature for given specifics, minimizing antisolvent and energy consumptions.

The occurrence of input multiplicity is, however, a problem from a control perspective, because it implies that the steady-state gains of the system may change sign as the system moves from one operating condition to another, therefore if a conventional feedback control is applied, it can lead to undesired output values, unstable or oscillatory responses (Kumar et al., 2005).

Development of suitable control strategies to deal with the input multiplicity for crystallization process is currently under study.

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