Growth rate estimation from online measurements of multidimensional particle size distributions

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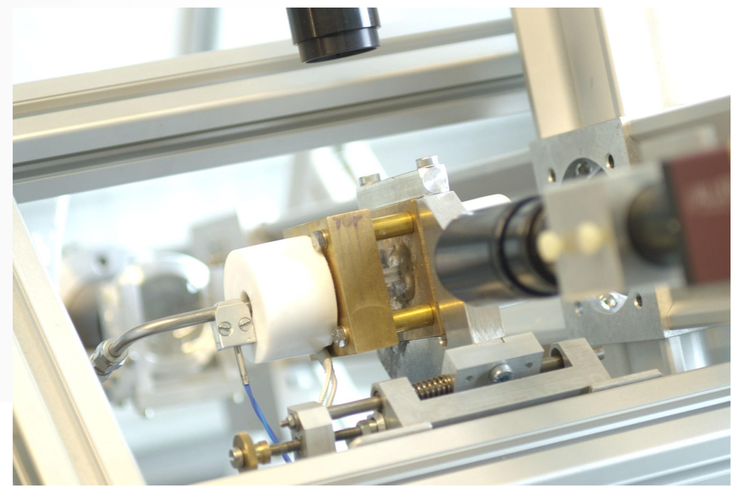


ABSTRACT

Particle size and morphology are important features of crystalline solids that influence a number of properties, e.g. flowability, tabletability and even bioavailability. Knowledge of the growth kinetics of all crystal facets would allow to optimise these properties, yet few have investigated growth rates of complex shaped crystals using populations of particles.

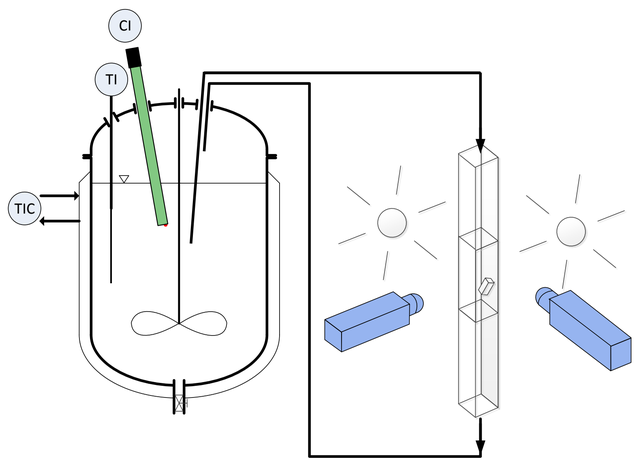
In this work, we have estimated growth kinetics of the needle shaped β polymorph of L-Glutamic acid in a wide range of process conditions based on measurements of multidimensional particle size distributions (*n*D PSDs), which were obtained online from an in-house built optical imaging setup [1-3].

The predictive quality of the fitted parameters, which are based on millions of particles, was tested successfully and a literature comparison was performed with satisfactory result.

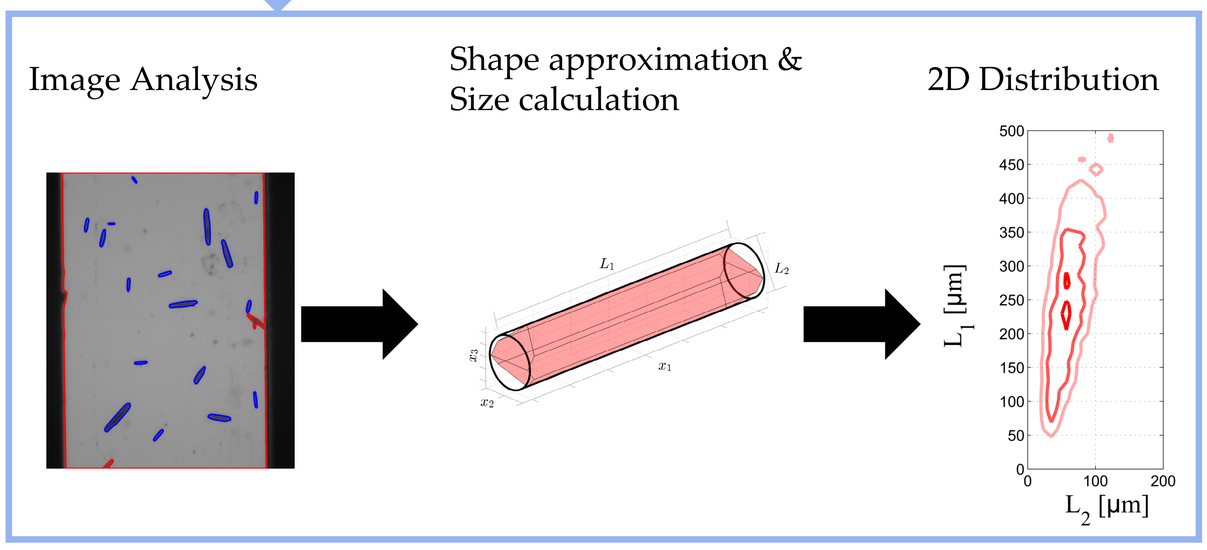
METHODS

Measurement and analysis

- Liquid concentration monitored using an ATR-FTIR probe



- Particles are sampled from reactor and photographed as they pass a flow through cell



Modeling and Estimation

The system is modeled using a 2D PBE with size independent growth only; coupled with a mass balance for the solute

$$\frac{\partial f(t,\boldsymbol{L})}{\partial t} + G_1(S,T;\boldsymbol{p})\frac{\partial f(t,\boldsymbol{L})}{\partial L_1} + G_2(S,T;\boldsymbol{p})\frac{\partial f(t,\boldsymbol{L})}{\partial L_2} = 0$$

$$\frac{dc}{dt} = -\rho_c k_v \frac{d\mu_{12}}{dt}$$

The maximum likelihood estimate is given by

$$p^{ML} = \arg\min \frac{N_t}{2}\sum_{i=1}^{N_v} \ln\left[\sum_{j=1}^{N_t}\left(y_{ij} - \hat{y}_{ij}(p)\right)^2\right]$$

Where the output y_j was chosen as

$$\boldsymbol{y}_j = \begin{bmatrix}\mu_{10}(t_j)/\mu_{00}(t_j) \\ c(t_j)\end{bmatrix}$$

EXPERIMENTS

- 11 seeded batch desupersaturation experiments were performed for the fitting (labeled 'FIT' in Figure 1)
- 2 additional experiments were conducted to verify the parameters (labeled 'VER' in Figure 1)

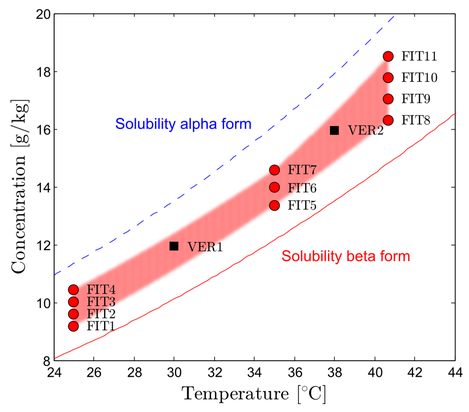


Figure 1: Experimental points in phase diagram

RESULTS

The best overall fit was obtained using a Birth and Spread type and an empirical expression

$$G_1(S,T,\boldsymbol{p}) = p_1 T \exp\left(-\frac{p_2}{T^2\ln(S)}\right)(S-1)^{2/3}\,(\ln(S))^{1/6}\exp\left(-\frac{p_3}{T}\right)$$

$$G_2(S,T,\boldsymbol{p}) = p_4(S-1)^{p_5}\exp\left(-\frac{p_6}{T}\right)$$

The maximum likelihood parameters and approximate 95% confidence intervals (Table 1) were found using all 11 experiments simultaneously (cf. Figure 2)

p_1^{ML} $[\mu m/Ks]$	2 ± 1
p_2^{ML} $[K^2]$	$5.2 \times 10^4 \pm 0.1 \times 10^4$
p_3^{ML} $[K]$	$2.5 \times 10^3 \pm 0.2 \times 10^3$
p_4^{ML} $[\mu m/s]$	$5 \times 10^4 \pm 6 \times 10^4$
p_5^{ML} $[-]$	2.9 ± 0.1
p_6^{ML} $[K]$	$3.8 \times 10^3 \pm 0.4 \times 10^3$

Table 1: MLE with 95% confidence intervals

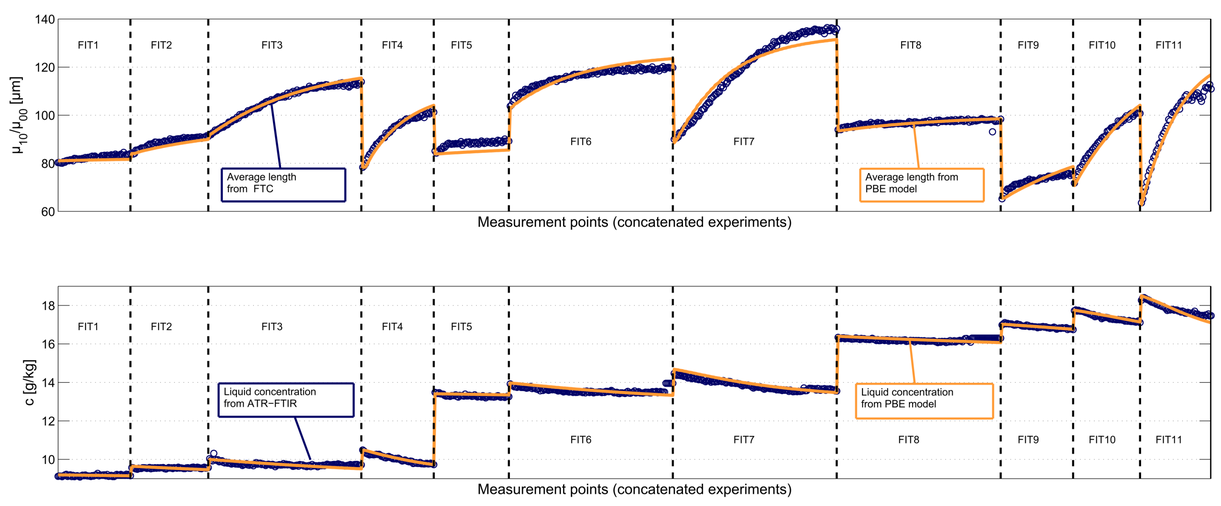


Figure 2: Measured and fitted outputs

The parameters were compared to literature (Figure 3) and the predictive potential was tested at two intermediate operating conditions (Figure 4)

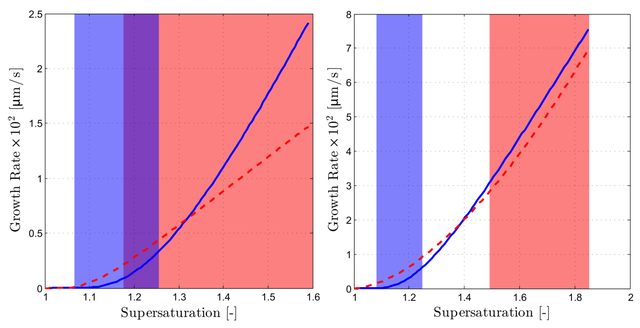


Figure 3: Growth rate comparison for the crystal length. Blue line: This work; Red dashed lines: Literature. Left: [4] ($T = 298$ K), Right: [5] ($T = 40$ °C, $L_1 \approx 100\ \mu m$)

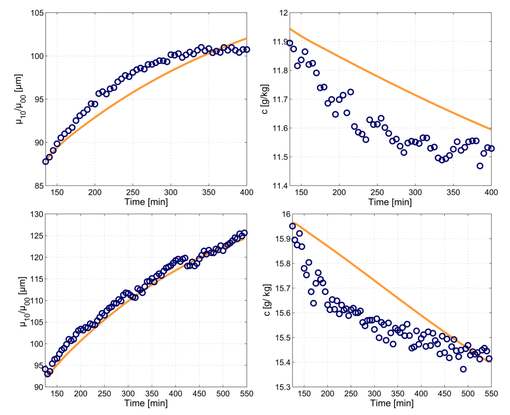


Figure 4: Verification Experiments

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