Dynamic Simulations of Continuous Plug Flow Crystallizer using gCRYSTAL

Aniruddha Majumder[1], Zoltan K. Nagy*[1,2], Niall Mitchell[3] and Sean K. Bermingham[3]

[1]Department of Chemical Engineering, Loughborough University, Loughborough LE11 3TU, UK
[2]School of Chemical Engineering, Purdue University, West Lafayette, IN 47907-2100, USA
[3]Process Systems Enterprise Ltd., London, UK

*Email: zknagy@purdue.edu

1. Motivation

- Over 90% of the active pharmaceutical ingredients (API) are crystals of small organic molecules
- Traditionally crystallization has been operated as batch process
- Continuous processing has benefits including consistency in product quality, reduction of cost by asset utilization, shorter down time and ease of scale up
- Continuous processing has been identified as key elements in improving manufacturing in pharmaceutical industries [1]
- gCRYSTAL provides an easy drag and drop simulation environment for simulation of crystallization processes
- Currently standard gCRYSTAL library does not include a plug flow crystallizer model that requires solving 2D population balance equation

2. Modeling of Continuous Plug Flow Crystallizer

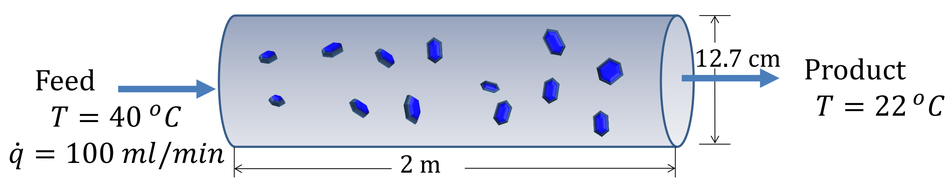


Figure 1: Plug flow crystallizer

- Plug flow crystallizer is one of the most common types of continuous crystallizer
- Assumptions: perfect mixing in radial direction, no mixing or dispersion in axial direction, density of the solution does not change
- Population balance modelling provides framework for describing crystallization process which can be written as

For growth and nucleation: $\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(u_x n) + \frac{\partial}{\partial L}(Gn) = J\delta(L - L_0);\ \ S \geq 0$

Kinetics [2]: $G(t) = K_{G0} \exp(-\frac{\Delta E_g}{RT})\ [1 - \exp\{-\alpha(L + \beta)\}]\, \sigma^g$

$$j_{prim} = j_a \exp[-\frac{j_b}{T^3 (\ln S)^2}];$$

$$j_{sec} = k_b M_T^j \Delta C^b; S = (C - C_{sat});$$

$$J = j_{prim} + j_{sec}$$

u_x is the mean flow velocity, n is the crystal size distribution, G is the growth rate, L is the crystal size, x is the position along the crystallizer, T is the temperature, J is the nucleation rate, S is the supersaturation ratio, σ is the relative supersaturation, M_T is the magma density, C is the concentration and $\alpha, \beta, K_{GO}, \Delta E_g,\ j_a, j_b, k_b, b, j$ are kinetic parameters

- Mass balance: $\frac{\partial C}{\partial t} + \frac{\partial}{\partial x}(u_x C) = -3\rho_s k_v G \int L^2 n dL$

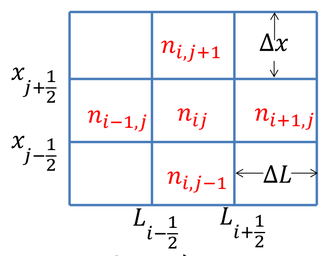
Performance index defined as

- Yield [%]$=\frac{C_0 - C(t_{end}, x_{end})}{C_0} \times 100$
- Average size $(\bar{L}_{43}) = \frac{\mu_4}{\mu_3}$; where $\mu_i = \int L^i n dL$

3. High Resolution Technique for Solving PBEs

- Finite volume method combined with van Leer flux limiter, also known as high resolution technique, used for discretization of the 2D PBE [3]
- Cell average of crystal size distribution (CSD) is taken as:

$$n_{ij} = \frac{1}{\Delta x \Delta L} \int_{x_{j-\frac{1}{2}}}^{x_{j+\frac{1}{2}}} \int_{L_{i-\frac{1}{2}}}^{L_{i+\frac{1}{2}}} n dL dx$$



- The PBE in each cell becomes an ODE

$$\frac{dn_{ij}}{dt} = -\frac{1}{\Delta L}\left(Gn|_{i+\frac{1}{2},j} - Gn|_{i-\frac{1}{2},j}\right) - \frac{1}{\Delta x}\left(u_x n|_{i,j+\frac{1}{2}} - u_x n|_{i,j-\frac{1}{2}}\right)$$

- Flux reconstruction at cell boundary: $n_{i+\frac{1}{2},j} = n_{i,j} + \frac{1}{2}\phi(r_{i+\frac{1}{2},j})(n_{i+1,j} - n_{i,j})$
- van Leer flux limiter to avoid oscillation near discontinuities

Flux limiter: $\phi(r_{i+1/2,j}) = \frac{|r_{i+1/2,j}| + r_{i+1/2,j}}{1 + |r_{i+1/2,j}|}$; $r_{i+1/2,j} = \frac{n_{i,j} - n_{i-1,j}}{n_{i+1,j} - n_{i,j}}$

4. Simulation Results using gCRYSTAL

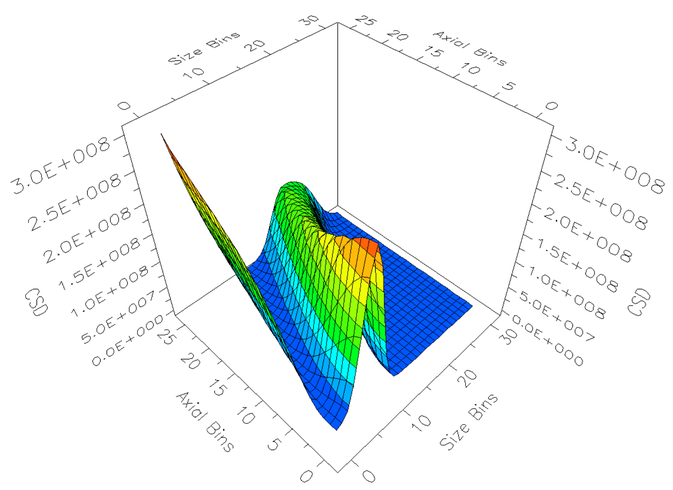


Figure 2: Final CSD along the FPC after 200 s when 2% seed mass is used.

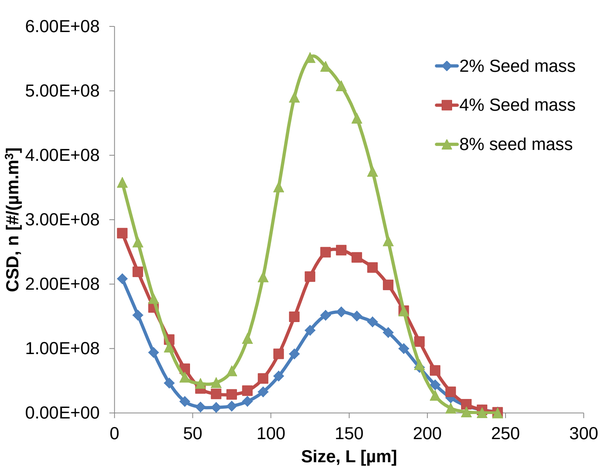


Figure 3: Comparison of the final CSD at the exit of the PFC after 200 s obtained for various seed mass used.

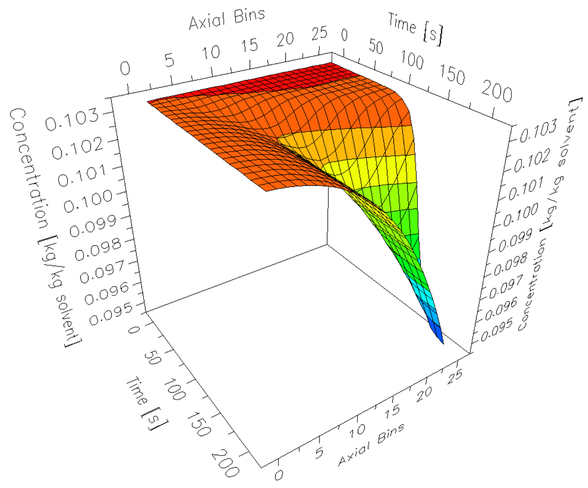


Figure 4: Evolution of the solute concentration profile along the PFC for 2% seed mass

Table 1: Summary of the results for various runs with different seed mass.

Run	Seed mass [%]	$\bar{L}_{43} = \frac{\mu_4}{\mu_3}$ [μm]	Yield [%]
1	2	170	8
2	4	168	14
3	8	152	20

5. Discussions

- Effect of seed loading is investigated on the average size of the crystal and yield of the process
- Figure 2 shows that the crystals not only grow in size, but also fine crystals appear due to nucleation
- Comparison of final CSD at the exit in Figure 3 shows that larger mean size is obtained for lower seed loading
- However, the yield of the crystallization increases as the seed loading increases due to higher solute consumption as shown in Table 1
- Concentration profile in Figure 4 shows the depletion due to crystal growth and nucleation along the PFC
- Work in progress to develop a more general PFC model that can handle multiple solutes, solvents and crystal phases

References

[1] Chen et al., *Cryst. Growth Des*. 2011, 11, pp. 887-895.
[2] Shoji et al., *J. Chem. Eng. Jap*. 2011, 44(3), pp. 191-196.
[3] Majumder and Nagy, *AIChE J.*, 2013, 59(12), pp. 4582-4594.

Acknowledgements

- Funding is acknowledged from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement No. [280106-CrySys]
- Process Systems Enterprise (PSE) Ltd. is acknowledged for providing gCRYSTAL software
- Funding from Eli lilly is acknowledged for supporting the 4 weeks visit to PSE Ltd., London