Exploiting limited sets of experimental measurements to calibrate models for batch cooling crystallization

Mauro Davanzo [a], Emanuele Tomba [b], Enrico Carlassare [b], Riccardo Motterle [b], Pierantonio Facco [a], Massimiliano Barolo [a] & Fabrizio Bezzo [a]

[a] CAPE-Lab - Computer-Aided Process Engineering Laboratory, Department of Industrial Engineering, University of Padova, via Marzolo 9, 35131 Padova PD, Italy

[b] F.I.S. Fabbrica Italiana Sintetici S.p.a., viale Milano 26, 36075 Montecchio Maggiore VI, Italy

E-mail: fabrizio.bezzo@unipd.it

The increasing demand in research efficiency and quality assurance for the design of pharmaceutical processes can find an answer in the application of model-based approaches to be used for simulation, optimization and scale-up of unit operations[1]. Crystallization is a core unit operation since it often serves as main separation step, and it is largely impacting on the product Critical Quality Attributes (CQAs). In this context, a key aspect is to be able to calibrate models that can reliably represent crystallizers at the large industrial scale, by exploiting information retrievable from the laboratory scale. This task can become notably challenging, in particular in those cases where datasets gathered from lab experiments present limitations related to the amount or nature of experimental measurements or to the experimental setup.

This work aims at obtaining models with good predictive capability for batch cooling crystallization outputs in an industrial context where limited datasets are available. To this purpose, a basic population balance model is defined as a starting point, including only nucleation and growth kinetic terms. The PharmaPy software is used as process simulator[2]. A paracetamol-water system is considered as a literature case study to validate the simulation capabilities of such tool. Also, the impact of different model parameters on the response is assessed thanks to sensitivity analysis. Subsequently, mathematical techniques for model parameter estimation is implemented and tested. We demonstrated that with an appropriate numerical setup, it is possible to achieve sufficiently precise estimations for nucleation and growth parameters based on in-silico generated data, despite significant amounts of noise and drift. Finally, the methodology is tested on experimental data collected in company's laboratories. The challenges related to the exploitation of real data are discussed, thus highlighting model shortcomings and the need to find suitable procedures to match simulation outputs with the amount and characteristics of industrially available measurements.

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