IFPRI Project Abstract

A Holistic Approach for the Model-based Control of Crystal Size, Shape and Purity in Integrated Batch and Continuous Crystallization - Wet Milling Systems

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Project Objective:

[2-3 sentence summary of original project brief]
The main objective of this project is the design of novel, integrated crystallization systems, which are able to produce increased control of the properties of crystalline materials, in the context of crystal size and shape distribution. The attainable region of crystal size distribution (CSD) is widened by the application of recirculation stream and by integrating wet mill for batch, and multiple MSMPR units and downstream wet mill with recirculation stream(s) for the continuous operation. 2D PBM based modeling, design and model-based control approaches are in the focus of this project, where the *in-situ* imaging based monitoring tools inherently has special importance.

Approach:

[2-3 sentence summary of project proposal (experimental/theoretical approaches)]
In this project a model based approach is applied, based on the use of comprehensive population balance (PB) framework. 1D and 2D PBM-s will be developed for the batch and continuous integrated systems, involving the high resolution finite volume method (HR-FVM) for the solution of generated model-equations. Kinetic model parameter estimation procedure is developed and carried out for the crystallization of a representative model API forming high aspect ratio crystals. Nonlinear model predictive control, involving the full 2D PBM will be developed and implemented using crystal shape information from the *in-situ* imaging tools.

Recent Results:

[Short summary of past year's progress and its significance, including one or two illustrative graphics (if useful)]

The portable crystallization solvers were extended with agglomeration and breakage mechanisms, involving at this stage the standard breakage selection and fragmentation, as well as agglomeration functions from the crystallization modeling literature. Extending the list of kernels (i.e. the dependency of rates on the agglomerating and breaking particle sizes) is going to be carried out.

In the first step along the line of development of integrated continuous crystallizer-wet milling systems model with multiple recirculation streams, a flexible MSMPR crystallizer cascade model has been developed, involving nucleation, growth, dissolution, breakage and agglomeration of 1D crystals for cooling, antisolvent and combined cooling and antisolvent crystallization pocesses. The importance of this simulation goes beyond the simulation of simple MSMPR cascades: it enables to model tubular systems as tank-in-series compartmental model. Given that there is no upper limit for the number of crystallizers and each crystallizer can be fed with both solute and antisolvent streams, this flexible solver enables the simulation of integrated MSMPR-tubular crystallizer systems in various configurations with single-or multi point antisolvent addition. This also paws the way for the MSMPR network solver, where certain MSMPR crystallizers can be operated as wet-mills or agglomerators not only in series but also in parallel configurations, with recirculation streams.

2D population balance models inherently involves more kinetic parameters then their 1D counterparts, and effective de-coupling of the nucleation from the length and width growth rates becomes crucial as the length and width growth parameters are inherently correlated *via* the mass balance. A new method has been developed to use the evolution of relative number density information coming either from *in-situ* imaging tools, or from the routinely used FBRM, needing no backward or forward CSD to/from CLD transformations. In essence, we aim to maximize the correlation between the simulated number density and the measured relative number density. With another words, we want to force the simulations to show increasing particle number trends where the e.g. the FBRM count increases and *vice-versa*, with (not necessarily linearly) proportional rates. This method has successfully been applied for two model-APIs (paracetamol crystallization from ethanol and another API, called Compound A crystallization). Moreover, the parameter estimation of the Compound A has already been initiated using 2D PBMs, as Compound A forms high aspect ratio crystals, and the shape is sensitive on the crystallization conditions indicating that the length and width growth/dissolution rates are independent, hence, has to be modelled separately. In this 2D parameter estimation the FBRM count, using the correlation maximization method, solute concentration evolution, Mastersizer CSDs (both for product and intermediates) as well as length and width distributions, extracted from optical microscopy images (for products and select intermediates) are being used the infer the crystallization kinetics by solving minimization problems.

Next Steps:

[2-3 sentence summary of where the project is headed in the next year. If the project is in its last year, a short summary of open questions.]

Blaze Metrics' imaging tool will be purchases by the end of this year, which will enable to carry out detailed comparisons with the Mettler Toledo's newest *in-situ* imaging probe, the EasyViewer, which is already in our laboratory. Furthermore, the MSMPR cascade simulation will be extended to 2D case, with nucleation, growth, dissolution and breakage mechanisms. Both 1D and 2D flexible MSMPR cascade solvers will be extended to flexible tank crystallizer network systems, that will also allow recircullations. The agglomeration and breakage mechanisms will be enabled or disabled in every crystallizer individually, which will allow to dedicate some tanks systems of the network to wet-mills. The 2D parameter estimation of nucleation, length and width growth and dissolution of the model API will be finalized.