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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1. Introduction. Importance of the topic

The prediction and control of crystal size, shape and purity distributions are necessary for product design, quality control and economical operation point of view. The desired crystal size, shape distributions and purity, largely depend on the application (Lovette et al., 2008). For example, needle-shaped (i.e., high-aspect-ratio) crystals are usually undesirable in pharmaceutical and fine chemical applications, due to difficulty in processing (Variankaval et al., 2008), while they are vital in applications such as synthesis of ZnO nanowires for solar cells (Law et al., 2005). Similarly, while generally in the production of active pharmaceutical ingredients (APIs) high purity is required, for certain food or consumer products (e.g. brown sugar) additives, in precisely controlled proportions, are included in the crystals by design. Moreover, some properties of the crystals such as catalytic activity, dissolution rate, hydrophobicity can be specific to certain crystal faces (Snyder et al., 2007) therefore additives can have a complex effect on crystal size, shape and purity.

This project is focused on the application of process systems engineering methods for the investigation of possibility of shape control of high aspect ratio crystals during solution crystallization. Remarkable results have been achieved in the first two years of the project, which will be further developed during the third year. However, given the process engineering knowledge accumulated so far by process simulations and model-based control implementations, it is evident that there is high potential, from both academic and industrial perspective, for designing and operating efficient, simple and high-performance crystallization processes for simultaneous crystal size and shape control.

2. Key achievements in the first two years

The following list of key achievements summarize the scientific output of the first two years of the project:

- Development of a portable, high performance (GPU accelerated) generic 1D and 2D PBM solver for batch and continuous (MSMPR) crystallization processes with primary and secondary nucleation, growth and dissolution mechanisms,
- Development of a fast, deep-neural network powered approximate 1D/2D CSD to CLD and ARD transformation for real time model-based control applications,
- Development of a NMPC algorithm for batch cooling crystallization processes involving CLD and concentration measurements and high accuracy full 1D PBM solution,
- Implementation of the aforementioned control algorithm for L-ascorbic acid, for which the state-of-the-art direct nucleation control (DNC) was not suitable, therefore, more advanced control strategy was required,
- Model development and GPU acceleration for an integrated crystallizer and wet-mill system for crystal size control (1D PBM) and combined crystal size and crystal shape control (2D PBM)
- Optimization based process synthesis for crystal size and combined size and shape control in integrated crystallizer – external wet mill using the afore described accurate models

These achievements have been disseminated in the following publications as measurable deliverables of the first two years of the poject:

(1) Szilágyi, B.; Borsos, Á.; Pal, K.; Nagy, Z. K. Experimental Implementation of a Quality-by-Control (QbC) Framework Using a Mechanistic PBM-Based Nonlinear Model Predictive Control Involving Chord Length Distribution Measurement for the Batch Cooling Crystallization of l-Ascorbic Acid. *Chem. Eng. Sci.* 2018. in press
(2) Szilágyi, B.; Agachi, P. Ş.; Nagy, Z. K. Chord Length Distribution Based Modeling and Adaptive Model Predictive Control of Batch Crystallization Processes Using High Fidelity Full Population Balance Models. *Ind. Eng. Chem. Res.* 2018, 57 (9).
(3) Szilagyi, B.; Nagy, Z. K. Optimization-Based Process Synthesis for Integrated Crystallizer-Wet Mill System for Improved Crystal Shape Control; *Computer Aided Chemical Engineering*, Vol. 43, 681-686, 2018.

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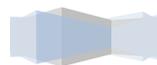
(4) Szilágyi, B.; Nagy, Z. K. Aspect Ratio Distribution and Chord Length Distribution Driven Modeling of Crystallization of Two-Dimensional Crystals for Real-Time Model-Based Applications. *Cryst. Growth Des.* , 18 (9), 5311-5321, 2018.
(5) Szilágyi, B.; Nagy, Z. K. Population Balance Modeling and Optimization of an Integrated Batch Crystallizer-Wet Mill System for Crystal Size Distribution Control. *Cryst. Growth Des*., 18 (3), 1415-1424, 2018.
(6) Szilagyi, B.; Borsos, A.; Simone, E.; Nagy, Z. K. Model Based Estimation of 2D Crystallization Kinetics From Concentration and CLD Measurements; *Computer Aided Chemical Engineering*, Vol. 40, 169-174, 2017

3. Projected results for the third year

Although the presentation of third year research plan is not the main subject of this proposal, a general summary will be given to provide an overall overview of the achievements of the entire three years period of the project and to put the proposed research directions for the project extension into better context. The third year will be focused on the shape manipulation of crystals during crystallization process. Three major objectives will be investigated:

- **2D MPC crystallization simulation**. A feasible, full 2D population balance model (PBM) based nonlinear model predictive control (NMPC) for cooling crystallization process will be developed, which will use experimental data coming from commercially available process analytical technology (PAT) tools, like concentration measurement, chord length distribution (CLD) and image analysis based mean aspect ratio. According to our best knowledge, there is no implementable full 2D PBM based NMPC system reported for crystal size and shape control yet.
- **2D crystallizer-wet mill configuration analysis**. Suring the first three years of the project it has been demonstrated that the integrated batch crystallizer – external wet mill system has high potential in simultaneous crystal size and shape control. The dynamic optimizer revealed an unexpected and interesting mode of operation, which, besides the clear application-oriented advantages, has high scientific value. However, there are numerous practical challenges for experimental implementation of the approach, associated mainly with the operation of pump and transfer lines. Therefore, at this stage it is reasonable to evaluate the relative performance of crystallizer-only, crystallizer with internal (immersion) milling and crystallizer with external mill for different operation modes (i.e. simultaneous size and shape control in seeded and unseeded crystallization).
- **IMED for spherical agglomeration.** Applying the correct kinetic model structure and finding its correct parameters is essential in model-based design. There are numerous, well analyzed methods to separate and investigate the kinetics of primary crystallization mechanisms (nucleation and growth), significantly less research effort was focused on the secondary crystallization mechanisms, such as agglomeration and breakage. Hence, the iterative model based experimental design (IMED) will be applied for a combined crystallization and spherical agglomeration process. In the first step a preliminary optimization will be applied to find the best kinetic model structure based on the available experimental data, then, in the second step, a precise parameter estimation will be carried out by executing additional experiments with maximal information content for minimizing the parameter uncertainty.

Projected publications for the third year:

1. European Symposium on Computer-Aided Process Engineering (ESCAPE) proceeding paper: "Real-time feasible model-based crystal size and shape control of crystallization processes"
2. Journal paper: "Iterative Model Based Experimental Design for Spherical Agglomeration Process"
3. Journal paper: "Model based analysis and optimization of crystallization of high aspect ratio crystal in the presence of immersion wet-milling and external wet-milling on the product particle size and shape"

4. Proposed project extension

In this section, a brief description of the project extension will be given, including the specific aims, list of deliverables and work plan. The "leverage into the PIs existing projects", "Broader impact" and "Collaboration with IFPRI member sections" form the original proposal are not repeated here.

Specific aims

This project extension aims to develop and provide the first proof-of-concept simulation and experimental demonstration of a full 2D PBM based NMPC approach for batch and continuous crystallization processes integrated with wet milling system, in order to achieve desired crystal size and shape distribution. Additionally, the effects of

impurity/additive mixtures on the size, shape and crystal purity distribution will be incorporated in the model and control design to provide a system that is highly relevant to industrial crystallization where the existence of impurities is rather the norm than the exception. To achieve this aim, the ***specific measurable objectives*** of the project are:

1. Extension of the recently developed, novel and highly efficient numerical solution platform for the 1D and 2D PBM using a parallelized discrete high resolution finite volume method (HR-FVM) solved on graphical processing units (GPUs) with fragmentation and agglomeration algorithms to provide a generic tool for high fidelity simulation of crystallization processes in presence of agglomeration and breakage mechanisms as well as basic level simulation of breakage only (e.g. milling) and agglomeration only (e.g. granulation) processes.

2. Develop a first-principle 2D PBM of the integrated continuous crystallization-wet milling system (C-CWM) with multiple MSMPRs and recirculation streams to optimize the MSMPR network structure and find the required recirculation scenario (recirculation configuration and recirculated amount).

3. Evaluate multiple input multiple output (MIMO) systems for advanced real time model-based crystal size and shape control, including the crystallizer+internal/external wet mill and crystallization in presence of impurities/growth rate modifiers.

4. Develop an imaging-based sensor for *in-situ* crystallization monitoring, for real time control applications. Compare the performance of the custom-probe with the standard imaging tools (e.g. Mettler-Toledo's ParticleView) and a novel tool (BlazeMetrics probe) for model-based crystal size and shape control applications.

5. Kinetic parameter estimation for the crystallization of a model compound in the most promising crystallization platform for crystal size and shape control and implementation of a full 2D PBM based NMPC.

Task 1. Include agglomeration and breakage into the portable, high performance finite volume based PBM solver. The portable 1D and 2D PBM solver, working based on fully-discretized serial and GPU accelerated HR-FVM, was developed for batch and MSMPR systems for primary and secondary nucleation, growth and dissolution. However, the solver does not consider agglomeration and breakage, which is a drawback for numerous industrial crystallization processes. Beyond advanced crystallization simulations, the agglomeration and breakage would also enable to simulate milling and granulation processes. The most typical empirical breakage and agglomeration kernels will be added to the portable solver and a generic PBM tool will be developed, which will be able to simulate all potential crystallization mechanisms and perform parameter identification and process optimization.

Task 2. Process synthesis and intensification of integrated continuous (MSMPR network) and wet mill system for simultaneous crystal size and shape control. The effectiveness of integrated crystallizer-wet mill system for both crystal size and combined crystal size and shape control has been shown, but the potential of wet milling in combination with an MSMPR network has not been exploited yet, even though MSMPR networks are widely used at industrial scale. In this study, the number of MSMPRs to add (up to three) to one wet mill, the position of wet-mill (pre-milling, intermediate milling or post-milling), mean residence times and circulation flowrates in the streams will be designed by optimization.
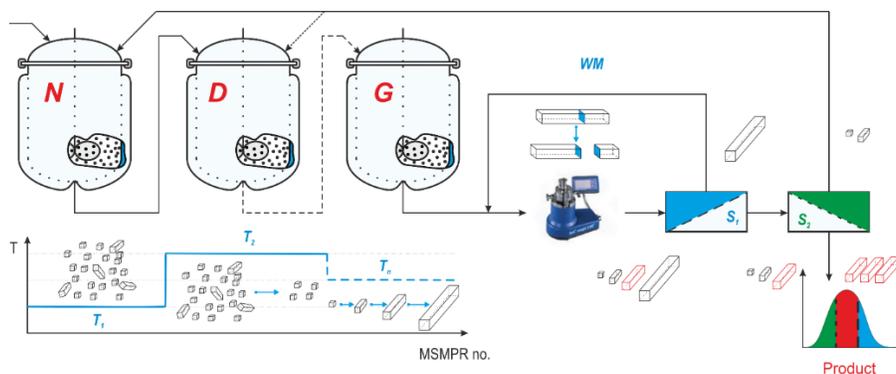
Fig. 1. Integrated continuous (cascade) of crystallization and wet mill system (C-CWM) with fine and course classification units and recycles. Optimizing the operating temperatures in the crystallizers enables to achieve spatially distributed controlled growth and dissolution cycles for improved control of CSD and ARD.

Task 3. Multi-impurity model and its possible application for model-based shape control. The effectiveness of external wet milling systems has been demonstrated by simulation, the powerful impact of growth-rate modifiers (GRM) were not profoundly investigated yet. GRMs with facet-specific effects is a very promising crystal shape modification technique. The practical problem associated with the application of GRMs is that in batch system the GRM concentration can be increased in time, but there is no straightforward solution to decrease it. Therefore, dosing the sufficient amount of growth rate modifier, without overshoot, is essential for effective control, which requires model based techniques for their predictive feature. Here the bottleneck is to capture the effect of growth rate modification well, using the most appropriate kinetic models and apply the required numerical acceleration techniques to make it suitable for real-time control applications.

Competitive adsorption model:
- multi-component (*j*)
- multi-site (*k*)
- multi-face (*i*)
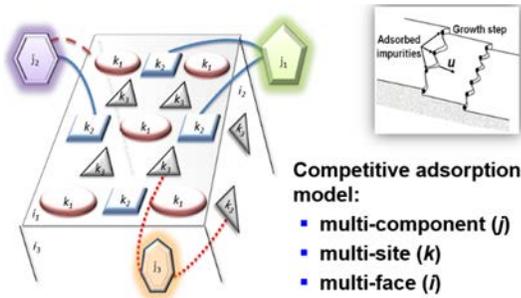
Fig. 2. Schematic representation of the modified crystal growth model using a multi-impurity multi-adsorption model (MIAM).

Task 4. Evaluation of various configurations and development of a model predictive control algorithm for crystal size control in crystallizer/(internal or external)wet mill system. The integrated crystallizer/wet mill system has high potential for crystal size control. The computational time with the current GPU acceleration may enable real-time control, which is required for efficient operation due to the highly uncertain nature of nucleation happening in the wet mill. The moving horizon estimator (MHE) will be tuned to account for the uncertainties (nucleation kinetics, effective breakage rate) and disturbances (temperature, concentration) raised under the milling conditions.

Task 5. Development of a low-cost imaging sensor for on-line crystal size and shape monitoring. The wider acceptance of the developed CSD and ARD control approach will depend on the availability of cost-effective image-based measurement systems, hence the development of a novel in situ stereo video probe, exploiting the recent progress in miniaturization, speed and quality of image processing hardware technologies. Initial proof of concept experiments was carried out in the PI's lab for the development of the dual imaging probe (Fig. 3) and the flexible budget provided by this grant would enable to development of a robust device for broader applications and potential commercialization.

Fig. 3. Schematic representation and preliminary designs of the mono- and stereo-CrystalEyes systems. A1 represents the gap for suspension (suspension flows through the gap in front of the camera lenses), and A2 represents the lens for the backlight (for more homogeneous background on images).
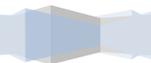
Task 6. Comparison and evaluation of *in-situ* imaging-based tools for on-line control applications. The real time model-based control has numerous application-specific requirements with respect to the measurement systems. The most typical limitations of the imaging probes, that are considered highly performant for system monitoring/off-line system analysis are the lack of real-time, flexible communication, lack of real-time running image analysis algorithm that enable the extraction of relevant particulate information for the NMPC and the high computational need for the image analysis, which overloads the CPU, slowing then down the machine, which is a significant limitation of calculation intensive NMPC algorithm. A control-oriented comparison of three probes, including our custom-designed, low-cost probe (CrystalEyes), the widely used imaging tool (Mettler-Toledo's ParticleView) and a state-of-the-art imaging probe (BlazeMetrics probe), that most recently appeared on the market, will be carried out for model-based crystal size and shape control applications. In addition to providing a recommendation and workflow for the use of imaging based crystallization measurements for 2D PBM model identification and model-based control, this task will also deliver a useful outcome by reporting the results of a detailed comparative investigation of several key imaging systems on the market for real-time quantitative crystallization monitoring and control, which will make the broader adoption of these systems across multiple process industries.

Task 7. Parameter estimation (nucleation, growth/dissolution along the specific axes), using the IMED procedure, for a 2D crystallization system. A critical piece of the NMPC is the process model, that can describe the dynamics of the process variables of interest accurately enough. The parameter estimation of high dimensional PBMs is challenging, because the multidimensional CSD cannot be directly measured with commercial PAT tools, which are typically available in an industrial environment. Subsets of information, such as liquid concentration, mean aspect ratio and FBRM count variation as well as equivalent spherical volume based CSD can be used for the parameter estimation. This, however, often transforms the optimization into an ill-conditioned problem, which requires the two-step IMED based parameter estimation to provide sufficiently accurate kinetic constants for the NMPC.

Task 8. Implementation of a 2D PBM based model predictive control for simultaneous crystal size and shape control. The most promising configuration from the simulation studies of Task 3 and Task 4, using the best shape measurement tool identified in Task 6 will be chosen to implement on a real crystallization system. The implementation is associated with numerous engineering challenges, from the significant effect of plant-model mismatch (PMM), through the uncertain and noisy nature of real time size and shape measurement to high computational power requirement to achieve real-time feasibility. These are the mean reasons why, to our best knowledge, there is no such an industrially relevant NMPC system implemented yet. We propose to develop the first such proof-of-concept experimental implementation of such a comprehensive advanced control approach.

Work plan

Detailed work plan and milestones are proposed in Table 1 and Table 2.

Table 1: Work Plan

Task	Activity	Years 1-3 (4-6 in overall)					
		6	12	18	24	30	36
1	Add agglomeration and breakage models into the high performance, portable 1D and 2D PBM solvers	▨					
2	Process synthesis of integrated continuous (MSMPR cascade) and wet mill system for simultaneous crystal size and shape control.	▨					
3	Multi-impurity model and it's possible application for model-based shape control			▨			
4	Evaluation of various configurations and development of a model predictive control algorithm for crystal size control in crystallizer/(internal/external)wet mill system.				▨		
5	Development of a low-cost imaging sensor for on-line crystal size and shape monitoring	▨	▨				
6	Comparison and evaluation of *in-situ* imaging-based tools for on-line control applications.			▨	▨		

7	Parameter estimation of the crystallization of a model-compound for simultaneous crystal size and shape control						
8	Implementation of a 2D PBM based model predictive control for simultaneous crystal size and shape control						

Table 2. Main milestones of the project

Month	Milestones
6	**(1)** Agglomeration and breakage functions in the portable PBM solver
12	**(2)** Process synthesis of integrated continuous (MSMPR cascade) and wet mill system for simultaneous crystal size and shape control.
24	**(3)** Multi-impurity model and it's possible application for model-based shape control **(4)** Evaluation of various configurations and development of a model predictive control algorithm for crystal size control in crystallizer/(internal/external)wet mill system. **(5)** Development of a low-cost imaging sensor for on-line crystal size and shape monitoring
30	**(6)** Comparison and evaluation of *in-situ* imaging-based tools for on-line control applications. **(7)** Parameter estimation of the crystallization of a model-compound for simultaneous crystal size and shape control
36	**(8)** Implementation of a 2D PBM based model predictive control for simultaneous crystal size and shape control

Main deliverables:

- A high performance, GPU accelerated portable 1D and 2D PBM solver extended with agglomeration and breakage.
- An optimized MSMPR/wet mill network for crystal size and shape control.
- Model based comparison of crystallizer with internal and external mill and crystallization in the presence of growth rate modifiers for real time model-based crystal shape control.
- Image analysis-based parameter estimation of multidimensional crystallization kinetics for a model-system.
- Implementation of a full 2D PBM based NMPC for crystal size and shape control.
- High quality journal and conference publications.

References

Lovette, M.A., Browning, A.R., Griffin, D.W., Sizemore, J.P., Snyder, R.C., Doherty, M.F., 2008, Crystal shape engineering, *Industrial & Engineering Chemistry Research*, 47, 9812-9833.

Variankaval, N., Cote, A.S., Doherty, M.F., 2008, From form to function: crystallization of active pharmaceutical ingredients, *AIChE J.*, 54, 1682-1688.

Snyder, R.C., Veesler, S., Doherty, M.F., 2008, The evolution of crystal shape during dissolution: predictions and experiments, *Crystal Growth & Design*, 8, 1100-1101.

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