

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

Rojan Parvaresh^a, Botond Szilagy^b

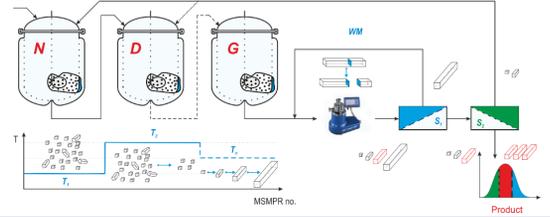
PI: Zoltan K. Nagy^{a*}

^a Davidson School of Chemical Engineering, Purdue University, West Lafayette, IN, USA

^b Department of Chemical and Environmental Process Engineering, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Budapest, Hungary

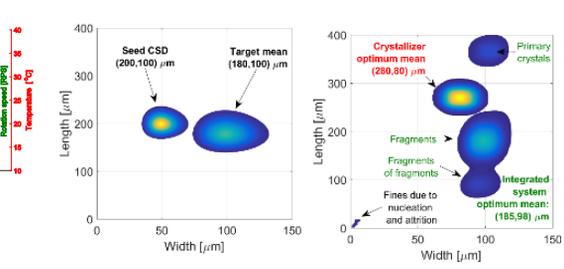
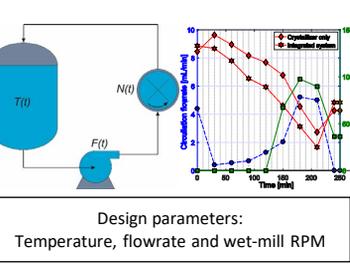
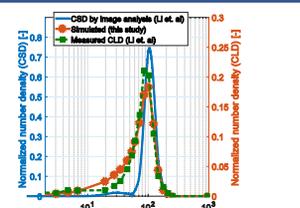
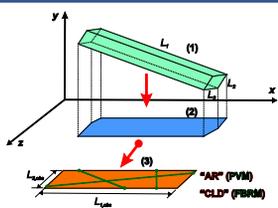
Specific aims: "To develop and provide the first proof-of-concept simulation and experimental demonstration of a real-time implementation of a full population balance model based nonlinear predictive control approach for batch and continuous crystallization processes integrated with wet milling and classification/recycle system, in order to achieve desired crystal size and shape distribution. The effects of impurity/additive mixtures on the size, shape and crystal purity distribution will be incorporated in the model."

- Crystallization-Milling-Classifier-Recycle systems (**Crys.-WM-Class.-R**)
- flexible crystallization network development
- Mechanisms:** 1D/2D nucleation, growth, dissolution, breakage, agglomeration
- Mean size increases with recycle
- Impurity increases with recycle
- CSD becomes broader with recycle



Objective

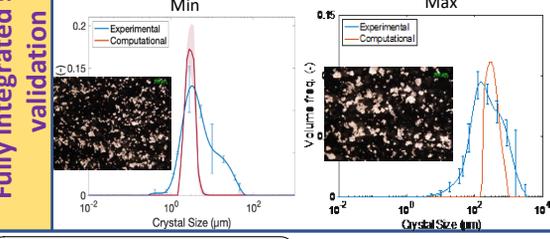
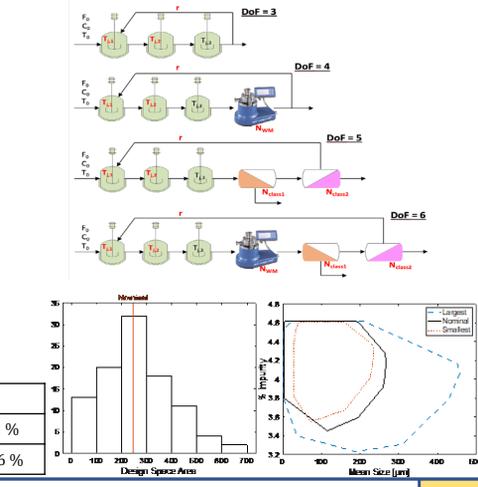
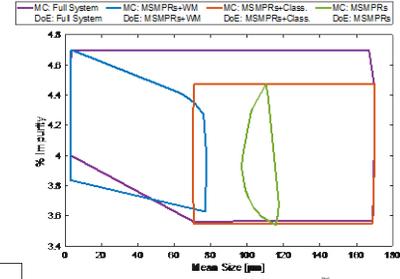
- High performance, **GPU accelerated** implementation of the HR-FVM for **1D and 2D** crystallization processes
- Soft sensor** based on improved geometrical model
- ANN** for learning the geometrical model output: efficient memory and **grid independent**.
- Estimation of measurable AR of a crystal population (PVM-soft sensor) from mean crystal size data.



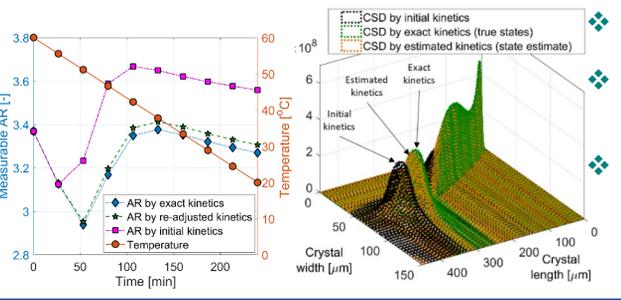
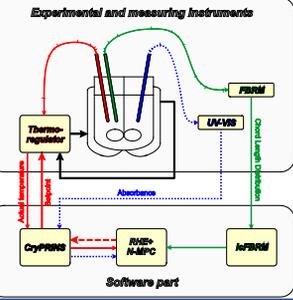
- External wet mill** in recirculation with batch crystallizer **High aspect ratio** crystals
- Mechanisms:** nucleation, growth, dissolution. Energy balance, fragmentation and attrition in the wet-mill
- Improved CSD** with the integrated system

Integrated crystallizer-wet mill

- Crys.-WM-Class.-R:** simplified
- Classifier design with **partition coefficient**
- Design space:** comparing 4 different integrated systems (DOE vs. Monte Carlo)
- Effect of **recycle** on COAs (mean size and impurity) and dynamics
- Validation experiments:** max and min mean size and impurity



	Min	Max
Impurity		
Experimental	3.95 ± 0.031 %	6.33 ± 0.012 %
Simulation	3.45 ± 0.016 %	4.62 ± 0.0086 %



- 1D kinetic parameter estimation, **1D NMPC** implementation (size control)
- IMED** based high performance parameter estimation for spherical crystallization (agglomeration)
- Real time feasible **2D NMPC** system development with sampling time < 5 minutes with 1 manipulated variable

NMPC development

Publications:

- Szilagy et al. *Software Balance Modeling and Optimization of an Integrated Batch Crystallizer-Wet Mill System for Crystal Size Distribution Control*, *Crys. Growth & Des.*; (2018)
- Szilagy et al. *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)
- Szilagy et al. *Aspect ratio distribution and chord length distribution driven modeling of crystallization of two-dimensional crystals for real-time model-based applications*, *Crys. Growth & Des.*; (2018)
- Szilagy et al. *Experimental implementation of 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.*; (2019)
- Szilagy et al. *Model-based analysis and Quality-by-Design framework for high aspect ratio crystals in crystallizer-wet mill systems using GPU acceleration enabled optimization*, *Comp. & Chem. Eng.*; (2019)
- Szilagy et al. *Real-time feasible model-based crystal size and shape control of crystallization processes*, *Comp. Aided Proc. Eng.*; (2019)
- Szilagy et al. *Application of model-based quality-by-control (QbC) for the efficient design of pharmaceutical crystallization processes*, *Crys. Growth & Des.*; (2020)
- Pal et al. *Iterative model based experimental design for spherical agglomeration process*, *AIChE J.*; (2021)
- Eren et al. *Optimization-based digital design of a commercial pharmaceutical crystallization process for size and shape control*, *Comp. & Chem. Eng.*; (2021)
- Wu et al. *Implementation and application of image analysis-based turbidity direct nucleation control for rapid agrochemical crystallization process design and scale-up*, *Ind. & Eng. Chem. Res.*; (2022)
- Parvaresh et al. *Digital Design of an Integrated Continuous Crystallization, Wet Milling and Classification System with Recycle*, manuscript in preparation

