

The CSD has a large impact on downstream processing and product efficacy for many crystallization processes, and is, therefore, often chosen as a controlled variable. There are many metrics for crystal size (*e.g.*, length, sieve diameter, volume diameter, surface diameter, projected diameter), which are often associated to a certain principle of measurement. The CSD is shaped by an interplay of various physical phenomena, which are driven by supersaturation and shear forces. Therefore, some form of supersaturation control at homogeneous hydrodynamic conditions is usually employed to obtain control over the CSD.

Process variables do not change anymore at steady-state conditions in the absence of disturbances, which simplifies control. Therefore, the majority of control approaches aims to keep controlled variables close to a desired set point at steady state. However, it has also been noted that steady-state operation for continuous crystallization may not necessarily be a goal by itself. For example, for pharmaceutical applications, it has been argued that not steady state but rather a “state-of-control” is needed.²⁶ Furthermore, in view of the possible high added value of raw materials and products and short campaigns (*e.g.*, for pharmaceutical applications), transient operational phases such as start-up and shut-down may have to be considered. For example, Patrascu and Barton^{27,28} demonstrated *via* dynamic optimization that optimizing a complete production campaign instead of only the steady-state operating point of an end-to-end continuous pharmaceutical manufacturing process including various crystallization steps can lead to a significant increase in productivity compared to when only considering steady state.

Powell *et al.*²⁴ introduced the periodic mixed-suspension mixed-product-removal (PMSMPR) crystallizer. In contrast to the conventional MSMPR crystallizer, product is transferred periodically from the crystallizer at high flow rates. A practical advantage of the PMSMPR crystallizer is that blockage in transfer lines can be minimized and classification in the product removal can be reduced due to the fast withdrawal of slurry. Selective removal of fines in the product outlet would not only violate the MSMPR concept, but could also lead to sustained oscillations.²⁹ A conceptual advantage of a seeded PMSMPR crystallizer is that the dynamic properties of the withdrawal cycle can be used as a manipulated variable to control CSD when PAT are available, which can be modeled.³⁰ They demonstrated that a multi-stage PMSMPR crystallizer system gave a better product quality in terms of size and shape compared to a single stage. Since the PMSMPR has dynamic properties that are comparable to batch operation, seeding is an important manipulated variable. Furthermore, the PMSMPR crystallizer reduces fouling, which can otherwise be an important practical problem for continuous crystallization. Dynamic operation for continuous crystallization can also be used to prevent fouling of a tubular crystallizer *via* model-based anti-fouling control by manipulating the properties of heating and cooling cycles.³¹ Finally, for a different type of application, such heating and cooling cycles can also be used to control crystal shape.³²