continuous or dispersed phase. For example, the aim can be to maintain operation within a certain supersaturation range (*i.e.*, between the solubility curve and the metastable limit) by manipulating the cooling duty, heating rate or anti-solvent addition rate. Such supersaturation control (SSC), also known as concentration control (C-control) or concentration feedback control (CFC) is simple and robust if suitable PAT is available. The SSC requires the measurement of concentration and a manipulated variable affecting the solubility of the system (*e.g.*, temperature, solvent/anti-solvent ratio) or solute concentration (*e.g.*, heat addition in case of evaporative crystallization). An optimal operating point requires an in-depth understanding of the crystallization mechanisms to mitigate the effects of nucleation or solid-state transitions. Another aim can be to control some property of the CSD directly. A traditional example is the use of a fines destruction loop, whereas a more recent approach is the so-called direct nucleation control (DNC) method that manipulates the kinetics of nucleation, growth, and dissolution through adaptive cooling and heating cycles.[61] The temperature cycles promote dissolution of the fines and growth of larger crystals, while reducing the width of the CSD, which is comparable to a fines dissolution strategy. The DNC has been extensively used for lab-scale crystallizers and demonstrated enhanced robustness and effective control over particle size, uniformity and polymorphic purity by eliminating fine particles and agglomeration.[62] Extensions to continuous crystallization are feasible in the case of plug-flow crystallizers, cascades of MSMPR crystallizers, or if additional actuation for heating is available in a single MSMPR.

The remainder of this section will discuss manipulated variables and illustrate typical feedback control loops that can operate without a process model. The available manipulated variables for continuous crystallization depend on the basic equipment configuration. Therefore, the discussion is organized by classifying the basic types of crystallizer hardware and their extensions.

4.4.1 MSMPR Crystallizer

Conventional continuous crystallizers such as the forced circulation crystallizer, DTB crystallizer, or the Oslo (fluidized-bed) crystallizer all aim to resemble the MSMPR concept. The advantages of MSMPR crystallizers are their robust operation and ability to provide the large residence times needed for crystallizing compounds with a slow growth rate or in case there is a need to produce large crystals. However, an MSMPR crystallizer operates at outlet conditions, which may limit attainable crystal growth rates, and inevitably leads to a high variability in the product quality due to the broad residence time distribution. Furthermore, the number of manipulated variables in a conventional MSMPR is limited. For example, consider a simple well-mixed jacketed draft-tube crystallizer operated in continuous flow mode for cooling crystallization as illustrated in Figure 4.1. There are two control valves present and possibly one variable speed drive. Therefore, we can construct three