

oscillates between rejecting and accepting the stationarity null hypothesis. By jointly analysing the unit-root and stationarity tests it can be stated that the process has reached stationarity after *ca.* 130 s. The Lilliefors and Jarque–Berra tests show that the data is normally distributed after 130 s, which is an indication of strict stationarity.

These results have shown that the hypothesis tests can be used to detect steady-state conditions on-line in a plug-flow crystallizer. The statistical framework described above can be applied to any continuously operated unit operation or sensor measurement. Besides on-line stationarity detection, the method described above can also be used as a steady-state “certificate”. In order to indicate that samples (solid or liquid) have been taken while the process was in stationary conditions, the probability of null-hypothesis acceptance p values returned by the unit-root, stationarity and normality tests should be documented and reported.

9.5 Model-free PAT-based Control Strategies

Model-free control strategies rely solely on the signals from PAT instruments and do not require any information about the kinetics of crystallization (*e.g.*, nucleation, growth, agglomeration) of the studied system. These feedback controllers can be used to achieve consistent product quality during batch and continuous crystallization. For continuous processes, PAT-based model-free control strategies have been used to achieve optimal crystal size distribution as well as crystal shape and polymorphism.¹⁸ FBRM, ATR-FTIR and UV/Vis are the most common instruments for model-free approaches, although Raman spectroscopy has also recently been used.¹¹ Automated direct nucleation control is a common strategy based on the use of an FBRM probe and the CryPRINS platform. The ADNC control approach is designed to keep the number of solid particles in a vessel constant during a crystallization process, using the FBRM signal and CryPRINS. Usually the total counts/s statistic is sent to CryPRINS and the temperature in the crystallizer is decreased if the measured total counts/s is lower than the setpoint range or increased if it is higher. In this way fine crystals in excess are dissolved and growth of the larger particles is promoted. The control method uses an algorithm with the following variables to be set: total counts setpoint, upper and lower total counts limits, proportional gains for the heating and cooling phase, maximum cooling and heating rates, and temperature at the end of the process. This strategy has recently been used for the operation optimization of MSMR crystallizers with and without a wet milling unit.^{4,6}

Model-free strategies have the advantage that they require little information about the controlled system. In fact, a full knowledge of the kinetics of every crystallization mechanism is not needed to develop a model-free approach. However, these techniques rely on the quality of the measured signal, which can be affected by fouling of the probes.