Input-Output State Feedback Linearization and Model Predictive Control of an MSMPR Crystalliser

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Introduction

The pharmaceutical industry has a growing interest in the capabilities of continuous manufacturing processes, which have significant advantages over traditional batch production methods, such as the reduction of waste, cost, footprint and lead-times. With the ongoing adoption of continuous technologies along with the Quality-by-Design paradigms, there is a demand for more robust and advanced process control strategies in the pharmaceutical industry [1]. The control of continuous crystallisation is particularly challenging due to the complexity of the underlying phenomena and their impact on the crystal size distribution and polymorphism, which in turn impact both downstream processing and the critical quality attributes of the final product. Model predictive control (MPC) has been extensively used in the oil and gas industry [2]. Nonlinear model predictive control (NMPC) was introduced later and has shown a lot of potential as an advanced control option for crystallization [3]. However, MPC is often less computationally intensive than NMPC and thus, is capable of encompassing a more detailed process into the control system, for real-time implementation, with the potential to ensure better critical quality attributes of the final product. The purpose of this research is to extend a previous application of input-output linearization MPC [4], by applying the method to a continuous crystallization system and by incorporating feasible constraints on the manipulated inputs; then the robustness of the controller is tested in the presence of system disturbances.

Methodology for Simulation

The system simulated is a 1 L continuous, single-stage MSMPR which is initially filled with saturated solution of API (paracetamol) in solvent (water) at 40 °C and seeded with 10 µm crystals. The absolute supersaturation of the API in the MSMPR crystalliser is chosen as the controlled output and the manipulated variable is the temperature of the coolant fluid in the jacket. The MSMPR model involves solution of the first four moment equations, derived from the dynamic population balance equation using the standard method of moments for kinetics representing secondary nucleation and size independent growth [5]; in addition, the dynamic mass and energy balances are also solved for the solution temperature and solute concentration. The process start-up is simulated to demonstrate that the MPC controller can achieve and maintain the desired supersaturation set-point without violating the constraints on the rate of temperature change of the coolant. Furthermore, to test the robustness of the controller, the feed flow rate, feed temperature and feed solute concentration into the system are perturbed to simulate input disturbances. Subsequently, the manipulated coolant temperature adjustments are monitored as the controller once again achieves the desired supersaturation.

Results and Conclusion

The results of the simulations established that the input-output linearized MPC is able to meet the desired supersaturation requirements using the coolant temperature as the manipulated variable. In the presence of disturbances to the feed flow, temperature and concentration, the controller is capable of rejecting small deviations from the steady state flow conditions without violating the coolant temperature constraints. However, drastic changes to feed conditions result in deviations in the supersaturation which cannot be controlled effectively with the coolant temperature alone, and a multi-input controller with additional inputs may be a better solution.

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