# State Feedback Linearization and Adaptive Model Predictive Control applied to a simulated MSMPR Crystalliser

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## Introduction

Continuous manufacturing processes have many advantages over batch methods, namely the reduction of footprint, waste, cost and lead-times. Consequently, the predominantly batch-operated pharmaceutical industry has interests in the capabilities of continuous manufacturing steps such as continuous crystallisation. In developing continuous technologies and adapting to a new Quality-by-Design (QbD) paradigm, there is a significant demand for control strategies that can ensure the critical quality attributes (CQAs) of the final product are maintained within tight regulations [1]. Model predictive control (MPC) and the nonlinear variant (NMPC) have been used extensively [2], mainly in the oil and gas industry [3], where it is evident that MPC is less computationally intensive than NMPC as a control method. This advantage is also present when using input-output state-feedback linearization, which enables the application of MPC to a nonlinear system [4]. The time reduction from using MPC offers greater potential for real-time control, or conversely, a more detailed process model can be incorporated into the control system, with the potential to ensure better CQAs of the final product. The purpose of this research is to extend a previous application of input-output linearization MPC [5], by applying the method to a continuous MSMPR crystallizer with realistic constraints on the manipulated input states. The novelty is to directly control the crystal size by assigning it as the controlled output, and to adapt a controller to a process by enhancing its internal model parameters in the presence of a process and model mismatch.

## Methodology

The simulated system 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 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 nucleation and size dependent growth [6]; in addition, the dynamic mass and energy balances are also solved for the solute concentration and solution temperature, respectively. Two simulation cases are presented based on real controller requirements and system behaviour. In scenarios where there is a mismatch between the MPC's internal model and the real process behaviour, there is an advantage in having an adaptive MPC which can adjust itself for better control of the system. Thus, the first case simulates an adaptive MPC which corrects itself in the presence of a growth parameter mismatch between the system and the controller's internal model. The controlled output is the absolute supersaturation and the manipulated input is the temperature of the coolant fluid in the crystalliser jacket. The growth rate is determined by eq.(1), where $C$ is the concentration of solute in the reactor, $C^*$ is the saturation concentration at the corresponding solution temperature and $k_g$ and $g$ are experimentally determined and fitted growth parameters.

$$G = k_g(C - C^*)^g \tag{1}$$

A mismatch in the growth parameter $g$ between the crystalliser model and the MPC's internal model is implemented at the start of the simulation. The criterion for mismatch is the deviation of the simulated process supersaturation from the MPC's past supersaturation horizon predictions, and if the error between these two values increases beyond an acceptable value, the MPC's prediction will not be accurate enough for control and a parameter fitting process is triggered inside the controller. The fitting process uses recent historical process data with a deterministic optimisation method to find a new acceptable value for $g$, which is then used in the MPC for future prediction.

One desirable CQA in the continuous crystalliser would be a unimodal crystal size distribution (CSD) with a consistent mean crystal size at the outlet. This is the motivation behind the second case, where the $L_{10}\left(\frac{\mu_1}{\mu_0}\right)$ mean size is controlled to a set-point value at steady-state and the manipulated input is again the temperature of the coolant fluid in the crystalliser jacket. Two simulations are provided, where the first

simulation is without disturbances to demonstrate the MPC can achieve the set-point during a transient start-up period to steady state and the second simulation introduces disturbances to the feed temperature to establish the MPC's disturbance rejection capabilities.

**Results and Conclusion**

The results show that a mismatch in the growth parameter $g$ creates a divergence in supersaturation from the set-point between the system's behaviour and controller prediction. Subsequently, the parameter fitting process is triggered and a new value for $g$ is successfully obtained and implemented; thereafter, the supersaturation set-point is maintained with no further divergence. For the second case, the $L_{10}$ mean size set-point is achieved successfully during the MSMPR start-up process and in the presence of feed temperature disturbances, the coolant temperature is adjusted to maintain the set-point, but there is still a significant variation in the mean size. The implication of these results is that a single-input single-output (SISO) controller in this configuration is not sufficient for crystal mean size control and consideration of a multiple-input multiple-output (MIMO) controller with additional manipulated inputs should present better control options and greater controller flexibility.

**References:**

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