

Application of MHE-based NMPC on a Rotary Tablet Press under Plant-Model Mismatch

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Abstract

Active control strategies play a vital role in modern pharmaceutical manufacturing. Automation and digitalization are revolutionizing the pharmaceutical industry and are particularly important in the shift from batch operations to continuous operation. Active control strategies provide real-time corrective actions when departures from quality targets are detected or even predicted. Under the concept of Quality-by-Control (QbC), a three-level hierarchical control structure can be applied to achieve effective setpoint tracking and disturbance rejection in the tablet manufacturing process through the development and implementation of a moving horizon estimation-based nonlinear model predictive control (MHE-NMPC) framework. When MHE is coupled with NMPC, historical data in the past time window together with real-time data from the sensor network enable model parameter updating and control. The adaptive model in the NMPC strategy compensates for process uncertainties, further reducing plant-model mismatch effects. The frequency and constraints of parameter updating in the MHE window should be determined cautiously to maintain control robustness when sensor measurements are degraded or unavailable. The practical applicability of the proposed MHE-NMPC framework is demonstrated via using a commercial scale tablet press, Natoli NP-400, to control tablet properties, where the nonlinear mechanistic models used in the framework can predict the essential powder properties and provide physical interpretations.

Keywords: pharmaceutical manufacturing; continuous manufacturing; process control; nonlinear model predictive control; moving horizon estimation.

1. Introduction

Several factors currently drive the transition of the pharmaceutical manufacturing industry from batch to continuous process operation. These include potential improvement in both product quality homogeneity and process controllability. Quality control traditionally followed a Quality-by-Testing (QbT) approach, wherein product quality was tested at the end of each batch processing step. However, with improved product and process understanding, a Quality-by-Design (QbD) approach was adopted to enable systematic design of the operating space using mechanistic models. More recently, there has been a desire to adopt a Quality-by-Control (QbC) approach, wherein quantitative and predictive understanding can be leveraged for active process control and aid robust process design and operation, thereby enabling smart manufacturing (Su et al., 2019).

An important part of any real-time process monitoring and control strategy is the ability to identify and manage the impact of plant-model mismatch (PMM). PMM can arise in the continuous manufacture of oral solid dosage for numerous reasons, e.g., disturbances that affect critical material attributes (CMAs) such as the bulk density can be introduced during the feeder refill step (Destro et al., 2021). As this can result in a deviation in the critical quality attributes (CQAs), PMM needs to be identified and handled appropriately. Several approaches have been developed in order to identify and assess the impact of PMM, e.g., based on mutual-information (Chen et al., 2013) or autocovariance (Wang et al., 2017). Stringent regulations placed by regulatory bodies make it essential to track CQAs and CMAs online, but they may be unmeasurable in practice as process analytical technology (PAT) sensing methods may not be available to track these states or parameters, e.g., bulk density. Therefore, this work proposes the use of an on-line, real-time parameter estimation approaches to accurately track model parameters online, to guide operating decisions. It is important to note that most work in the continuous manufacturing domain utilize linear model predictive control (MPC) strategies, that are derived from the linearization of the nonlinear system and may not be adequate for nonlinear process models and unit operations such as the rotary tablet press (Ierapetritou et al., 2016).

A recent in-silico study by (Huang et al., 2021) demonstrated that a combined MHE-NMPC framework could satisfy the dual requirement of efficient estimation and control. Unfortunately, there are no case studies in the literature that demonstrate the application of the proposed framework to real data from a continuous pharmaceutical manufacturing process. Therefore, the primary objective of this work is to validate the practical applicability of the proposed framework using a Natoli NP-400 rotary tablet press.

2. Methodology

The moving horizon estimation-based nonlinear model predictive framework (MHE-NMPC) aims to satisfy the dual requirement of estimation and control, by combining the effective estimation capabilities of MHE with the control performance provided by NMPC. Given a nonlinear state-space model:

$$\dot{x} = g(x, u, \theta, w) \quad (1)$$

$$y = l(x, u, \theta, v) \quad (2)$$

where x , u , θ , and y are vectors that represent the state variables, input variables, model parameters, and measurements, respectively. Process and measurement noise are denoted by w and v , respectively. In this work, the model is described by a set of explicit algebraic equations with no differential states, and f and h will represent these algebraic equations. MHE can then be formulated as follows (López-Negrete and Biegler, 2012):

$$\min_{\hat{\theta}_k} J = \sum_{t=k-N_{past}}^k (\epsilon_t)^T W_E \epsilon_t + (\hat{\theta}_k - \hat{\theta}_{k-1})^T W_\theta (\hat{\theta}_k - \hat{\theta}_{k-1}) \quad (3a)$$

subject to

$$\hat{x}_{k-N_{past}+j+1} = f(\hat{x}_{k-N_{past}+j}, u_{k-N_{past}+j}, \hat{\theta}_k) \quad (3b)$$

$$\hat{y}_{k-N_{past}+j} = h(\hat{x}_{k-N_{past}+j}) \quad (3c)$$

$$\epsilon_{k-N_{past}+j} = y_{k-N_{past}+j} - \hat{y}_{k-N_{past}+j} \quad (3d)$$

$$\hat{x}_{k-N_{past}+j+1} \in \mathbb{X}, \quad \epsilon_{k-N_{past}+j} \in \Omega_{\epsilon}, \quad \hat{\theta}_k \in \Omega_{\theta} \quad (3e)$$

$$j = 0, 1, \dots, N_{past} \quad (3f)$$

where $\hat{\theta}_k$ are estimated uncertain parameters, bounded in compact set Ω_{θ} . y_t and u_t are measurements of output and input variables at time t , respectively; $\hat{y}_t$ and $\hat{x}_t$ are estimated output and state values, respectively; ϵ_t are output disturbances, bounded in compact set Ω_{ϵ} ; and W_E and W_{θ} are weighting matrices. Once the MHE optimization problem is solved at time $t = k$, the estimated state $\hat{x}_{k-N_{past}+1|t=k}$ is chosen as the initial state value for the next time step $t = k + 1$, i.e., $\hat{x}_{k-N_{past}+1|t=k+1} = \hat{x}_{k-N_{past}+1|t=k}$.

This study utilizes the median of the error distribution in the past time window to represent output disturbances ζ_k at time $t = k$, i.e.,

$$\zeta_k = \text{median}\{\epsilon_{k-N_{past}+j}\}, \quad \text{for } j = 0, 1, \dots, N_{past} \quad (4)$$

The NMPC framework at time $t = k$ is defined as follows:

$$\min_{\Delta u_t} J = \sum_{t=k}^{k+N_p} (\hat{y}_t - y_{sp})^T W_y (\hat{y}_t - y_{sp}) + \sum_{t=k}^{k+N_c-1} (\Delta u_t^T W_{\Delta u} \Delta u_t) \quad (5a)$$

subject to

$$\hat{x}_{k+j+1} = f(\hat{x}_{k+j}, \hat{u}_{k+j}, \hat{\theta}_k) \quad (5b)$$

$$\hat{y}_{k+j} = h(\hat{x}_{k+j}) + \zeta_k \quad (5c)$$

$$\Delta u_{k+j} = \hat{u}_{k+j+1} - \hat{u}_{k+j} \quad (5d)$$

$$\hat{x}_{k+j} \in \mathbb{X}, \quad \hat{u}_{k+j} \in \mathbb{U}, \quad \Delta u_{k+j} \in \Omega_{\Delta u} \quad (5e)$$

$$j = 0, 1, \dots, N_p - 1 \quad (5f)$$

where N_c is the length of the control time window, and y_{sp} are the setpoints of the output variables. W_y and $W_{\Delta u}$ are weighting matrices. Control movements Δu are constrained in compact set $\Omega_{\Delta u}$. A detailed discussion of the MHE-NMPC framework including its computational feasibility is provided in (Huang et al., 2021).

3. Case Study

3.1. Tablet press model

The tablet press is responsible for the formation of solid tablets via mechanical compression. The weight of a convex tablet W and the tablet production rate $\dot{m}_{\text{tablet}}$ are given by the following relationships (Huang et al., 2021):

$$W = \rho_b V_{\text{fill}} \left(1 - \xi_1 \frac{n_T}{n_F} + \xi_2 \frac{H_{\text{fill}}}{D} \right) \quad (6)$$

$$\dot{m}_{\text{tablet}} = W n_T N_{\text{station}} \quad (7)$$

where D , V_{fill} , H_{fill} , ρ_b , n_T , and n_F , are the diameter of the die, volume of the die cavity, dosing position, powder bulk density, turret speed, and feed frame speed, respectively. N_{station} refers to the number of stations in the tablet press. ξ_1 and ξ_2 are empirical model parameters that are estimated from experimental data. The volume of the die cavity for the D-type tooling is provided by (Huang et al., 2021).

The pre-compression force F_{pc} and the main compression force F_{punch} can be computed as follows:

$$F_{pc} = \frac{\pi D^2}{4b} \left[\frac{\rho^{pc} - \rho_c}{\rho^{pc(a-1)} + \rho_c} \right] \quad (8)$$

$$\rho^{pc} = \frac{W}{V^{pc} \rho_t} \quad (9)$$

$$F_{punch} = \frac{\pi D^2}{4b} \left[\frac{\rho^{in-die} - \rho_c}{\rho^{in-die(a-1)} + \rho_c} \right] \quad (10)$$

$$\rho^{in-die} = \frac{W}{V^{in-die} \rho_t} \quad (11)$$

where parameters a and b are Kawakita constants, which represent the maximum degree of compression and the reciprocal of the pressure applied to attain this degree of compression, respectively. ρ^{pc} and ρ^{in-die} are the pre-compression and in-die relative densities, respectively. ρ_t refers to the true density of the powder. The pre-compression volume, V^{pc} , and in-die volume V^{in-die} are provided by (Huang et al., 2021).

3.2. Applying MHE to tablet press: Comparison of fixed model and adaptive model

To investigate state estimation and parameter updating, an experiment was performed via open-loop control. Setpoint changes of input variables were introduced to the tablet press, and corresponding measurements of output variables and model predictions are recorded and shown in Figure 1 (a) with fixed model parameters and Figure 1 (b) with adaptive model parameters.

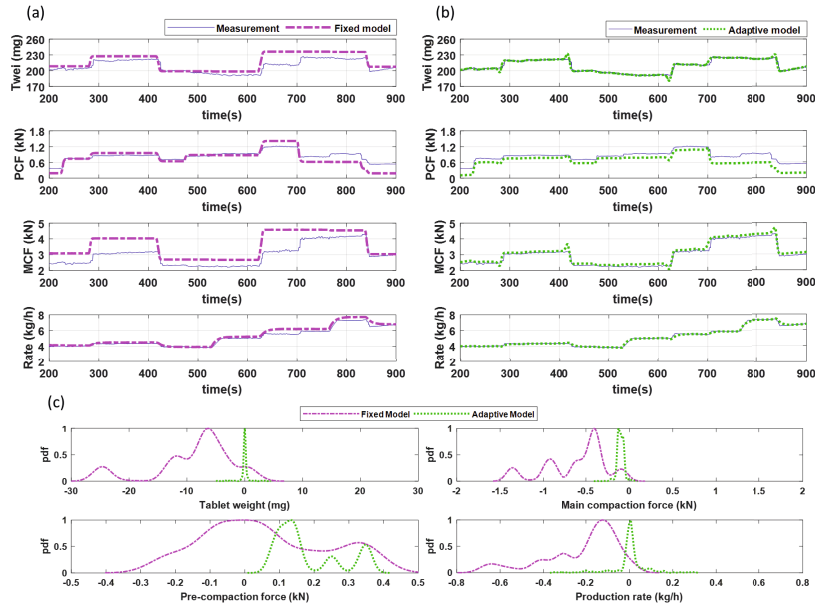


Figure 1. Real-time monitoring of PMM when uncertain parameters are (a) fixed or (b) adaptive with (c) error distribution of estimated output variables.

In this study, since the mathematical model is represented by a set of explicit algebraic equations the MHE only updates two uncertain parameters: (1) the bulk density (ρ_{bulk}),

to compensate for the effects of disturbance on the estimated value of the tablet weight, which further affects estimated values of pre-compression force, main compression force, and the production rate, and (2) the critical relative density (ρ_c) to provide flexibility to estimate the pre-compression and main compression forces more accurately in the adaptive model compared to the case of only bulk density being updated. The adaptive model predicts output variables more accurately compared to the fixed model.

To quantify model accuracy and precision, error distributions of the estimated output variables are provided in Figure 1 (c), where the probability density functions (pdf) of the error distributions are rescaled (meaning that the area under the density curve is not 1). Once MHE is applied to update the bulk and critical relative densities, the absolute values of the median error and error spans of all output estimations are significantly reduced, as shown in Figure 1 (c). However, an exception is found in pre-compression force, whose error span is reduced from 0.75 kN to 0.37 kN, while median error is increased from 0.07 kN to 0.22 kN. Since pre-compression force and main compression force share the same model parameters as shown in Equation (8-11), there exists the need to establish a compromise between the accuracy of these two output variables.

3.3. Experimental verification of MHE-NMPC

Control profiles for a representative experimental run of the 4 input variables, 4 output variables, and 2 uncertain model parameters are shown in Figure 2 (a), (b), and (c), respectively. Offsets in the output variables are observed as open-loop control is applied at the start of operation (highlighted in red). When the MHE-NMPC algorithm is implemented from $t = 200$ s, offset free control is achieved. Additional setpoint changes are introduced for the tablet weight at $t = 600$ s, 800 s, 1500 s, the main compression force at $t = 1100$ s, and the production rate at $t = 1000$ s.

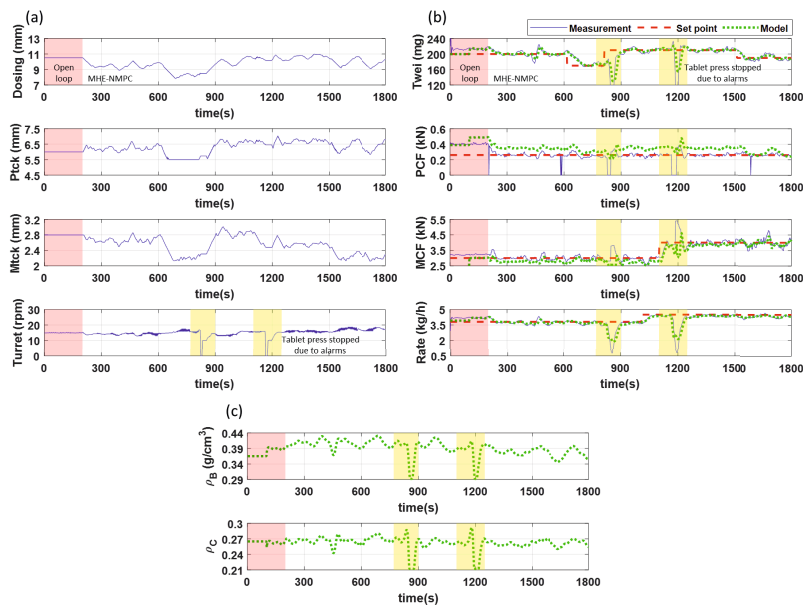


Figure 2. MHE-NMPC control performance of the tablet press with (a) input variables, (b) output variables, and (c) uncertain parameters.

All results of setpoint tracking are satisfactory as shown in Figure 2 (b). During the experimental run, an internal alarm stopped the tablet press twice at $t = 820$ s and $t = 1160$ s (highlighted in yellow) forcing the turret speed to drop to 0 rpm. The machine stop prevents the distributed control system (DCS) from collecting in-house tablet weight and production rate measurements, where the time delay can be attributed to the 10 s moving average window. The strength of the MHE-NMPC algorithm can once again be noted, as offset-free control is quickly achieved once the tablet press resumes operation. As the uncertain parameters are updated in real-time as shown in Figure 2 (c), the mismatch can be mitigated as presented in Figure 2 (b). While mismatch for pre-compression force cannot be completely mitigated, as it shares the same parameters as the main compression force, the disturbance term used in controller model described in Equation 5c still guarantees offset-free control of the pre-compression force.

4. Conclusions

Real-time process monitoring and control are essential to enable continuous operation of modern pharmaceutical manufacturing processes. The MHE-NMPC framework demonstrates satisfactory control performance and parameter updating in the rotary tablet press to handle plant-model mismatch (PMM). Future work will include sensor fusion studies to incorporate at-line measurements with long sampling time to the framework. Accurate estimation is required to enable the control of critical quality attributes such as tensile strength, which need to be predicted from soft sensors due to limited availability of real-time measurements because of the destructive nature of the testing methods used.

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