Development of an Artificial Intelligence Based Predictive Controller for a Continuous Pharmaceutical Manufacturing Process

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Abstract

One of the advantages of continuous manufacturing (CM) is that advanced process control tools can be incorporated in the control strategy for achieving a better quality control when compared to the traditional batch processes. However, the utilizations of CM with advanced process control in the pharmaceutical industry are still not common. In addition, FDA has recognized CM and its associated risks on product quality as one of its research focuses that has been laid down in its strategic plan since 2011. Development of digital twin models has the potential to enhance FDA's ability to evaluate the risks associated with latest advanced process control systems by providing the reviewers with powerful tools that facilities the assessment (e.g., robustness and reliability) of advanced process control (APC) strategies submitted in sponsor's applications. In this study, a feed-forward neural network predictive control (NNPC) model was developed and trained using a digital twin of a controlled plant. The digital twin, which acts as an analog of the actual plant, was constructed based on the residence time distribution (RTD) theory in continuous stirred-tank reactor (CSTR). Simulation results demonstrated the excellent performance of the NNPC in terms of two process control scenarios, i.e., set point tracking and disturbance rejection, in comparison with the traditional PID controller. The simulation results exhibit the potential of the utilization of the NNPC model in the pharmaceutical CM process. In conclusion, the numerical model developed in this work can provide the reviewers with necessary information and knowledge on the risks of using advanced process controls in CM and the impacts on the product quality.

Introduction

The modernization of pharmaceutical manufacturing through the adoption of innovative approaches has the potential to improve the efficiency and quality of drug production. Continuous manufacturing (CM) is an innovation that enables production in an interconnected process, potentially reducing production costs, lowering material inventory, and allowing for smaller-scale productions. The use of digital twins in CM allows for the development and application of multi-physics, multi-scale, probabilistic simulations, leading to growth in modeling and simulation data submitted to support CM applications. The fourth industrial revolution, or Industry 4.0, brings integrated, autonomous, and self-organizing production systems that potentially increase output, improve quality, and reduce waste. Artificial intelligence (AI) is a disruptive Industry 4.0 technology, with AI-based advanced predictive control allowing dynamic control of processes to achieve desired output and high product quality. AI methods can also be used to develop process controls that can predict the progression of a process in combination with real-time measurements of critical quality attributes (CQAs) using process analytical technology (PAT). However, the implementation of innovative technologies may represent challenges to the industry. The FDA plays a critical role in supporting and regulating the adoption of these technologies to protect and promote public health. The FDA is also developing and leveraging modeling and simulation tools to assess these applications. As of April 2023, the FDA has approved eight solid oral drug products that utilized CM, demonstrating the growing interest and adoption of this approach within the pharmaceutical industry. It is essential to establish the credibility of the models and maintain high product quality when implementing these technologies. Development of digital twin models increases the FDA capacity for evaluating the risks associated with APC systems and provides the reviewers powerful tools that facilities their assessments.

Materials and Methods

In this work, the NNPC used a feed-forward neural network (Fig. 1) to represent a nonlinear system for predicting future performance of the system. A digital twin model based on residence time distribution (RTD) theory was applied to perform training, validation and testing of the neural network for a CM process (Fig. 2). Then, the predictive control was carried out based on receding horizon method (Fig. 3). A conventional PID controller was also developed for the CM process to quantitatively compare with the NNPC model regarding several performance parameters, such as overshoot, rise time, settling time, and peak deviation (Eqs. (1-5)).

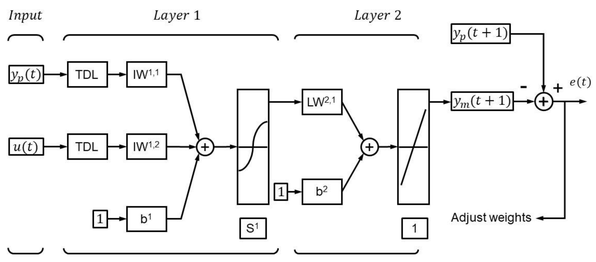

Figure 1. Structure of the neural network plant model

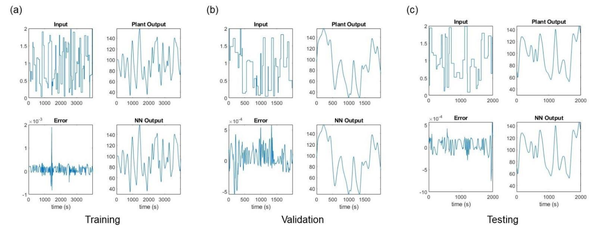

Figure 2. Neural network (a) training, (b) validation, and (c) testing results

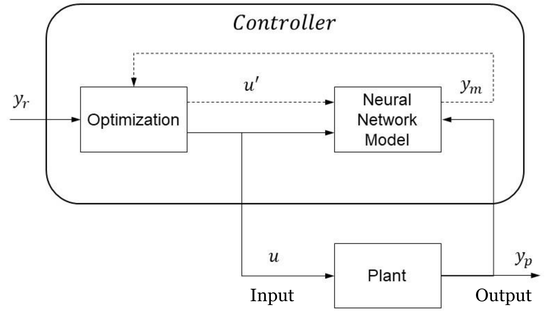

Figure 3. Schematic diagram of the NN-based predictive controller

Results and Discussion

Response assessment is required for two main aspects: set-point tracking (Fig. 4) and disturbance rejection (Fig. 5). In a closed-loop system, set-point tracking involves the assessment of the controlled variable response to a change in desired set point, e.g., outlet concentration, while disturbance rejection involves the assessment of any process variable's response to a disturbance in its value, e.g., input concentration or flow rate. Three metrics were chosen to assess set-point tracking in this study, i.e., overshoot δ, rise time τ_r and settling time τ_s (Table 1). Two metrics were chosen to assess disturbance rejection, i.e., peak deviation ε and settling time τ_d (Table 2).

$$\delta = \frac{|\sigma_{max} - C^*_{ref}|}{C^*_{ref}} \times 100\% \quad (1)$$

$$\tau_r = T(C_{out-plant} = 90\%\, C^*_{ref}) - T(C_{out-plant} = 10\% C^*_{ref}) \quad (2)$$

$$\tau_s = T\left(\frac{|C_{out-plant} - C^*_{ref}|}{C^*_{ref}} \le 2\%\right) - T(C^*_{ref,0}) \quad (3)$$

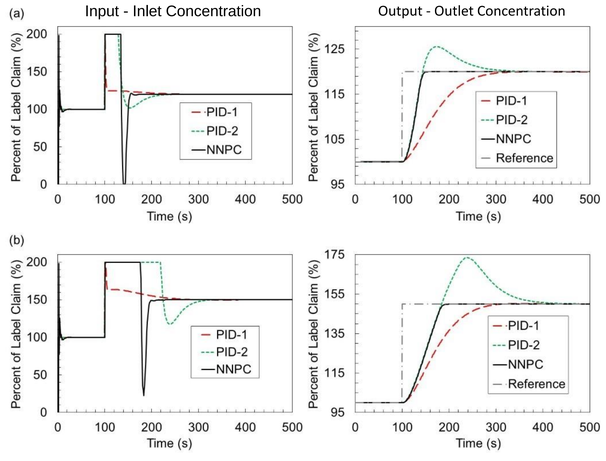

Figure 4. Comparison between NNPC and PID models control results regarding set-point change: (a) D = 20% and (b) D = 50%

Table 1. Response assessment regarding set-point changes.

	δ (%)	τ_r (s)	τ_s (s)
	C^*_{ref} = 20%		
PID-1	0	121.85	193.52
PID-2	27.80	28.69	200.04
NNPC	0	28.49	45.62
	C^*_{ref} = 50%		
PID-1	0	116.74	182.63
PID-2	46.90	58.41	287.85
NNPC	0	58.43	85.32

$$\varepsilon = \frac{|\varepsilon_{max} - C_{ref}|}{C_{ref}} \times 100\% \quad (4)$$

$$\tau_d = T\left(\frac{|C_{out-plant} - C_{ref}|}{C_{ref}} \le 2\%\right) - T(D_0) \quad (5)$$

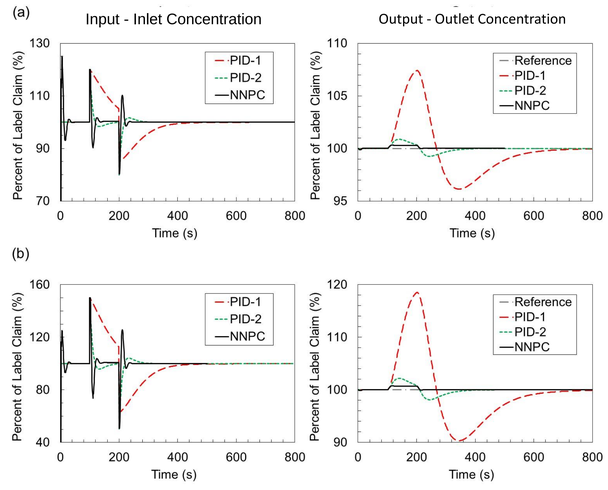

Figure 5. Comparison between NNPC and PID models control results regarding disturbance rejection: (a) D = 20% and (b) D = 50%,

Table 2. Response assessment regarding disturbance rejection.

	ε (%)	τ_d (s)
	D = 20%	
PID-1	37.1	485.5
PID-2	4.3	189.7
NNPC	1.6	0
	D = 50%	
PID-1	37.1	485.8
PID-2	4.4	189.8
NNPC	1.56	0

Conclusion

In conclusion, this study highlights the potential of incorporating APC tools into a pharmaceutical CM process. By doing so, the developer may achieve a better quality control and process efficiency. The NNPC model can inform the reviewers on the risks of utilizing APCs in CM and their impacts on the drug product CQAs.

Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.