



Proactive-residence time distribution method for determining low-risk setpoints of critical material attributes in pharmaceutical continuous manufacturing

Pasindu Herath Pathirannahalage^a, Ayumu Nabetani^a, Shota Kato^a, Kanta Sato^b, Keita Yaginuma^b, Shuichi Tanabe^b, Manabu Kano^{a,*}

^a Department of Informatics, Kyoto University, Yoshida-Honmachi, Sakyo-ku, Kyoto, 606-8501, Japan

^b Formulation Technology Research Laboratories, Daiichi Sankyo Co., Ltd., 1-12-1, Shinomiya, Hiratsuka, 254-0014, Japan

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ABSTRACT

In recent years, the pharmaceutical manufacturing industry has been working towards adopting continuous manufacturing of drug product to improve productivity. However, the complexity of integrated processes makes quality assurance difficult. In pharmaceutical manufacturing, the required product quality is achieved by maintaining the critical material attributes (CMAs) within a region called the design space (DS). To keep the CMAs within the DS, their feedback control plays a critical role, and proper determination of their setpoints is crucial. In the present work, we propose the proactive-residence time distribution (P-RTD) method, which determines setpoints based on the prediction of the effective CMAs calculated using RTD functions. We compared the performance of the P-RTD method and those of the other three methods through control simulations of realistic continuous dry granulation lines. Besides, we conducted simulations under various conditions varying the relationships among CMAs and the lag times of the processes. The results showed that only the P-RTD method kept the CMAs within the DS under all conditions.

1. Introduction

Throughout the past decades, the pharmaceutical industry has been undergoing a shift from batch to continuous manufacturing of drug product. When compared to other process industries, overall processes are predominantly relying on batch manufacturing and exhibit less efficiency (Myerson et al., 2015). Continuous manufacturing offers several key advantages over batch manufacturing including streamlined manufacturing timeline (Almaya et al., 2017; Nasr et al., 2017), flexible production volumes (Burcham et al., 2018), enhanced product quality (Fisher et al., 2016; O'Connor et al., 2016; Rantanen and Khinast, 2015) and reduced manufacturing costs (Li et al., 2016; Seifert et al., 2012; Tsukanov et al., 2016). These merits make continuous manufacturing a promising technology that can overcome challenges, such as unnecessary product recalls and drug shortages, and modernize pharmaceutical manufacturing (O'Connor and Lee, 2017). However, due to the difficulties in understanding disturbance propagations in integrated processes, quality assurance has been a challenge of continuous manufacturing (Tian et al., 2019).

Product quality in pharmaceutical manufacturing relies on the ability to consistently maintain critical quality attributes (CQAs) within

established tolerable ranges. The ICH Q10 guideline recommends the establishment and maintenance of a state that provides assurance of continued process performance and product quality for pharmaceutical manufacturing (International Council for Harmonisation, 2008). To achieve this state, the Quality-by-Design (QbD) approach, which promotes designing processes that can systematically ensure the quality of intermediate products, is utilized. In the QbD approach, pharmaceutical quality is assured by sustaining the critical process parameters (CPPs) and critical material attributes (CMAs), which have a substantial impact on CQAs, within a design space (DS). The DS is defined as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality” (International Council for Harmonisation, 2009). The DS is an integral part of the QbD approach that provides a better understanding of processes and enhanced regulatory flexibility (Kusumo et al., 2020). Extensive research has been carried out on the DS for pharmaceuticals. Bano et al. (2018) determined a CMA and CPP-based DS using latent-variable modeling in combination with multivariate Bayesian regression. A CPP-based

* Corresponding author.

E-mail address: manabu@human.sys.i.kyoto-u.ac.jp (M. Kano).

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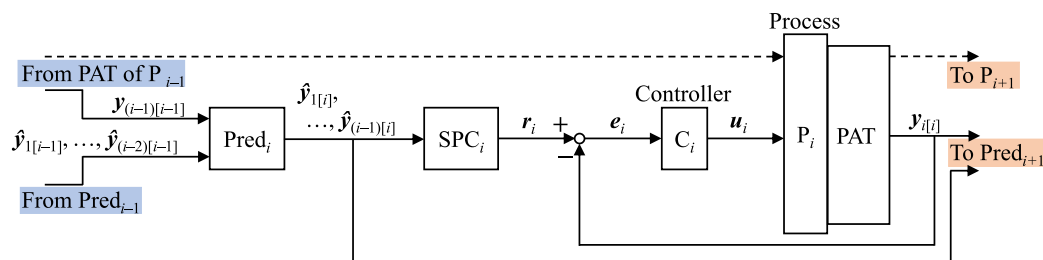


Fig. 1. Block diagram of the control system of the i th process, P_i . $y_{(i-1)[i-1]}$: measured CMAs of P_{i-1} at the outlet of P_{i-1} , $\hat{y}_{1[i-1]}, \dots, \hat{y}_{(i-2)[i-1]}$: predicted CMAs of preceding processes of P_{i-1} at the outlet of P_{i-1} , Pred_i : CMA predictor of P_i , SPC_i : setpoint calculator of P_i , r_i : setpoints of the CMAs of P_i , e_i : control errors of P_i , C_i : controller of P_i , u_i : CPPs of P_i , PAT : process analytical technology, $y_{i[i]}$: measured CMAs of P_i at the outlet of P_i . The dashed arrows represent the flow of materials, and the solid arrows represent the flow of information.

DS was formed by Assegehegn et al. (2020) for the primary drying section of a freeze-drying process. Rosas et al. (2011) defined a CPP-based DS for the production of a pharmaceutical gel. Chatzizaharia and Hatzivramidis (2015) determined a CMA-based DS for the production of a generic oral drug using a multi-regression and multi-response optimization model. Chavez et al. (2015) proposed a CMA-based DS using a risk-based Bayesian predictive approach to optimize a tablet formulation. Tanabe et al. (2023) created extensive and flexible low-dimensional CPP-based and CMA-based greedy DSs using high-dimensional data. Moreover, Nakagawa et al. (2015) demonstrated a CMA-based enhanced QbD approach, which was approved in April 2011 in Japan.

A CMA-based DS is sufficient to assure pharmaceutical quality since fluctuations of CPPs affect CQAs through CMAs. While the CMA is not defined by ICH, there is a description for the practical contribution of in-process material attributes to CQAs in ICH Q8(R2): “CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product”. Yu et al. (2014) further clarified the contribution of the in-process material attributes to CQAs. They defined the in-process material attribute as a CMA for a downstream manufacturing step, suggesting a logical workflow of CPP-CMA-CQA in the manufacturing process train. A CMA-based QbD approach offers robust quality control since it can eliminate the effect of noise in monitoring and controlling CPPs.

The ICH Q13 outlines scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing (CM) processes for drug substances and drug products (International Council for Harmonisation, 2022). While CM offers potential benefits such as improved efficiency and product quality, it also presents unique challenges in ensuring consistent product quality, particularly due to the integrated nature of continuous processes and the need for real-time monitoring and control. A robust control strategy is paramount to keep CMAs within the DS. Numerous studies have been dedicated to examining control strategies for pharmaceutical continuous manufacturing. Pauli et al. (2018) applied a variable rate control strategy to twin-screw wet granulation and continuous fluid-bed drying processes of a continuous manufacturing line. Jelsch et al. (2021) presented a comparison between conventional control tools, such as proportional integral derivative (PID) controllers, and model predictive control (MPC). Lakerveld et al. (2015) demonstrated a practical application of an automated control strategy in a continuous pharmaceutical pilot plant. Ishimoto et al. (2021) outlined a methodology for developing a control strategy tailored to the continuous manufacturing of oral solid dosage forms. Dahlgren et al. (2019) discussed the development of effective control strategies for continuous wet granulation, aiming to facilitate its widespread utilization.

Controlling CMAs within the DS in continuous manufacturing is an arduous task due to challenges including variability of raw materials and sensitivity of processes to environmental conditions such as heat, light and pressure. The key to addressing these issues is to determine appropriate setpoints of CMAs in the DS. Although the

CMA-based control strategy is a useful method that can diminish the effects of disturbances, there are some points to pay attention to when implementing it in continuous manufacturing. Batch manufacturing allows the CMA measurements of a representative sample to be used in subsequent processes, whereas continuous manufacturing does not because the materials are redistributed depending on the retention in the following processes. In addition, each manufacturing operation is generally destructive and thereby makes it impossible to re-measure the CMAs of the preceding processes. Therefore, controlling all CMAs within the DS requires accurate tracking of material distribution and process control based on that information. In this study, we propose the proactive-residence time distribution (P-RTD) method, which dynamically determines setpoints of CMAs of multiple processes using RTD functions. The RTD represents the probability distribution of the time a material is likely to remain in a process (Viitanen, 2005). RTD can also be used to estimate the redistribution of CMAs. In continuous manufacturing, determining setpoints in a multi-dimensional DS formed by multiple CMAs is challenging. When relationships among the CMAs are complex, it is difficult to sustain the CMAs within the DS. We show that the proposed P-RTD method excels in sustaining the CMAs within the DS by conducting control simulations assuming realistic continuous dry granulation lines with varying relationships among CMAs and lag times of processes.

2. Method

Consider a pharmaceutical continuous manufacturing line composed of a series of I processes, P_i ($i = 1, 2, \dots, I$), where the setpoints for the target process, P_T ($T = 2, 3, \dots, I$), are to be determined. In this study, variations of CMAs of P_1 are considered as unavoidable disturbances. The P-RTD method has two major steps. The first step is to predict the CMAs of preceding processes, P_i ($i = 1, 2, \dots, T-1$), at the outlet of P_T using the RTD function of P_T . The second step is to determine the setpoints of the CMAs of P_T so that they have the least chance of falling outside the DS.

The block diagram of the control system of P_i is illustrated in Fig. 1. Suppose that P_i has a total of N_i CMAs to be controlled, represented by $y_i = [y_{i,1}, y_{i,2}, \dots, y_{i,N_i}]^T$, and a total of M_i CPPs, represented by $u_i = [u_{i,1}, u_{i,2}, \dots, u_{i,M_i}]^T$, to be manipulated by the controller C_i . The notation $y_{i[k]}(t)$ represents y_i at the outlet of P_k at time t and their predicted values are represented by $\hat{y}_{i[k]}(t)$.

2.1. CMA prediction

CMA prediction using RTD functions is the first step of the P-RTD method. For quality assurance, CMAs of P_T , $y_{T[T]}$, as well as CMAs of upstream processes, $y_{i[T]}$ ($i = 1, 2, \dots, T-1$), must be within the DS. The CMAs of $y_{i[T]}$ are different from measured CMAs, $y_{i[i]}$, since materials pass through one or more processes following their RTDs. In general, PAT measures only $y_{i[i]}$ because it is specifically designed to validate the quality of intermediate products once they leave P_i (Rathore et al.,

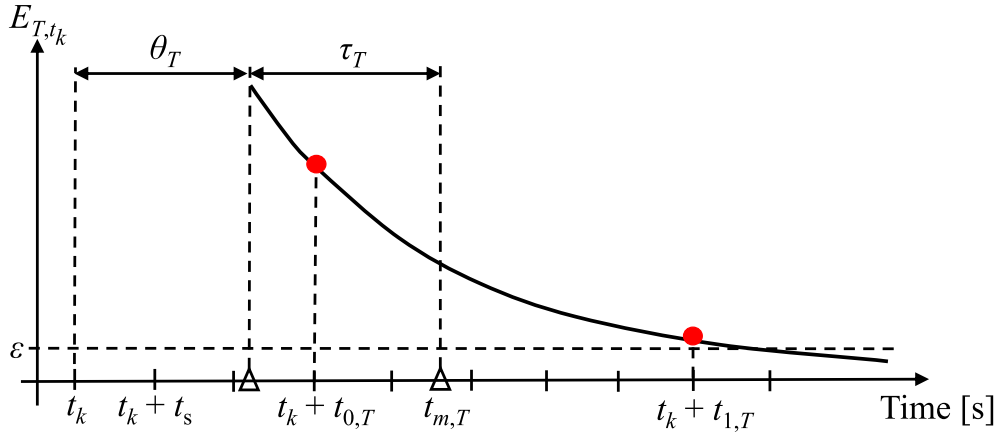


Fig. 2. A residence time distribution (RTD) function, $E_{T,t_k}(t)$, of materials that enter the target process, P_T , at sampling time t_k , with threshold ϵ . Triangles represent times that do not necessarily coincide with sampling times. t_s : sampling interval, θ_T : lag time of P_T , $t_k + t_{0,T}$: immediate sampling time after $t_k + \theta_T$ above the threshold, $t_{m,T}$: mean residence time (MRT) of P_T , τ_T : parameter related to the MRT of P_T , $t_k + t_{1,T}$: maximum sampling time above the threshold.

Table 1

Definition of symbols used in Eq. (1).

Symbol	Definition
$\hat{y}_{(T-1),j[T]}(t)$	Predicted j th CMA of P_{T-1} at the outlet of P_T at t
$E_{T,t_k}(t)$	RTD function of materials that enter P_T at sampling time t_k
$y_{(T-1),j[T-1]}(t_k)$	Measured j th CMA of P_{T-1} at sampling time t_k

2010; Read et al., 2010). The CMA predictor of P_T , Pred_T , calculates $\hat{y}_{i[T]} (i = 1, 2, \dots, T-1)$ using $\hat{y}_{i[T-1]} (i = 1, 2, \dots, T-2)$ and $y_{(T-1),j[T-1]}$.

It is assumed that the mass flow rates at the inlet and outlet of a process are equal and there is no material retention between two consecutive processes, meaning that once materials are discharged from P_i , they enter P_{i+1} without any delay. The lag time θ_i corresponds to the time taken by a material introduced to P_i to initiate its discharge from P_i . Suppose that the RTD function of materials that enter P_T at sampling time $t_k (k = 1, 2, \dots)$ is denoted by $E_{T,t_k}(t)$. Sampling time t_k refer to the times at which samples of materials are collected, and CMAs are measured. To mitigate excessive computational expenses associated with storing many $E_{T,t_k}(t)$ values in memory, we disregarded any values below the threshold ϵ in this study. Fig. 2 presents $E_{T,t_k}(t)$ given by a combined model comprising one plug flow reactor (PFR) and one continuous stirred tank reactor (CSTR). When materials enter P_T at t_k , they begin to leave the process at $t_k + \theta_T$. The first sampling time following $t_k + \theta_T$ that satisfies $E_{T,t_k}(t) \geq \epsilon$ and the last sampling time that satisfies $E_{T,t_k}(t) \geq \epsilon$ are denoted as $t_k + t_{0,T}$ and $t_k + t_{1,T}$, respectively. Only the $E_{T,t_k}(t)$ values between $t_k + t_{0,T}$ and $t_k + t_{1,T}$ are used in calculations.

At each sampling time t_k , PAT measures $y_{(T-1),j[T-1]}(t_k)$ immediately after materials have exited P_{T-1} . Let the j th components of $y_{i[k]}(t)$ and $\hat{y}_{i[k]}(t)$ be $y_{i,j[k]}(t)$ and $\hat{y}_{i,j[k]}(t)$, respectively. $\hat{y}_{(T-1),j[T]}(t)$ is computed using $y_{(T-1),j[T-1]}(t_k)$ of materials that were introduced into P_T between $t - t_{1,T}$ and $t - t_{0,T}$ as follows:

$$\hat{y}_{(T-1),j[T]}(t) = \frac{\sum_{t_k=t-t_{1,T}}^{t-t_{0,T}} E_{T,t_k}(t) y_{(T-1),j[T-1]}(t_k)}{\sum_{t_k=t-t_{1,T}}^{t-t_{0,T}} E_{T,t_k}(t)} \quad (1)$$

Table 1 summarizes the definitions of the symbols used in Eq. (1). Eq. (1) shows the weighted average of the CMA, $y_{(T-1),j[T-1]}$, at different sampling times before t . The weights are the RTD function values at t , $E_{T,t_k}(t)$. Fig. 3 illustrates an example of $y_{(T-1),j[T-1]}(t)$ and its respective $E_{T,t_k}(t)$ to be used in Eq. (1). In Eq. (1), the recent $y_{(T-1),j[T-1]}(t_k)$ between $t - t_{0,T}$ and t are not utilized. Those recently measured values can be utilized by advancing the interval of t_k , from $t - t_{1,T}$ to $t - t_{0,T}$, by $t_{0,T}$ forward. This provides $\hat{y}_{(T-1),j[T]}(t+t_{0,T})$. In most cases, the sampling

interval t_s is sufficiently small, and ϵ is chosen small. Thus, $t_{0,T}$ can be regarded as θ_T , and $\hat{y}_{(T-1),j[T]}(t+t_{0,T})$ becomes approximately equal to $\hat{y}_{(T-1),j[T]}(t+\theta_T)$.

Eq. (1) assumes linear superposition of CMA for simplicity. When this assumption is not valid due to strong nonlinear interactions, Eq. (1) needs to be modified.

2.2. Setpoint determination

The second step of the P-RTD method is setpoint determination. Throughout this study, the DS is specified a priori as an n-dimensional parallelotope. If the true DS is non-orthogonal or curved, the largest inscribed parallelotope is extracted and used as the ‘Original DS.’ This representation allows each overlap operation to be performed via simple component-wise interval reduction. The setpoint calculator of P_T , SPC_T , determines the setpoints of y_T , $r_T = [r_{T,1}, r_{T,2}, \dots, r_{T,N_T}]$, ensuring that y_T are less likely to deviate from the DS. The setpoints are determined by calculating the center of gravity of relevant points in the DS.

Algorithm 1 explains how $r_T(t)$ are determined. An example of setpoint determination is shown in Fig. 4. The algorithm requires the DS and $\hat{y}_{i[T]}(t+\theta_T) (i = 1, 2, \dots, T-1)$ as inputs. Each $\hat{y}_{i,j[T]}(t+\theta_T)$ forms a hyperplane in the multi-dimensional space encompassing the DS. There is overlap among the hyperplanes. Let R_i be the overlapping region of $\hat{y}_{i[T]}(t+\theta_T)$. First, the restricted DS (RDS) is defined as the original DS. In the for loop, i is set to 1, and whether R_i and the RDS overlap is checked. If they overlap, the overlapping region is redefined as the RDS. Otherwise, the RDS is kept unchanged. Then, the same steps are followed for the next iteration of i until $i = T-1$. After the for loop, the center of gravity of the vertices (vertex) of the resultant RDS, C , is calculated. Finally, coordinates of C which correspond to y_T are set as r_T .

Algorithm 1 Setpoint determination method

Require: DS and $\hat{y}_{i[T]}(t+\theta_T) (i = 1, 2, \dots, T-1)$
 Restricted DS (RDS) $\leftarrow$ Original DS
for $i = 1$ to $T-1$ **do**
 $R_i \leftarrow$ Overlapping region of $\hat{y}_{i[T]}(t+\theta_T)$
 if R_i and the RDS overlap **then**
 RDS $\leftarrow$ Overlapping region of R_i and the RDS
 else
 Keep the RDS unchanged
 end if
end for
 $C \leftarrow$ Center of gravity of the vertices (vertex) of the RDS
 $r_T \leftarrow$ Coordinates of C which correspond to y_T

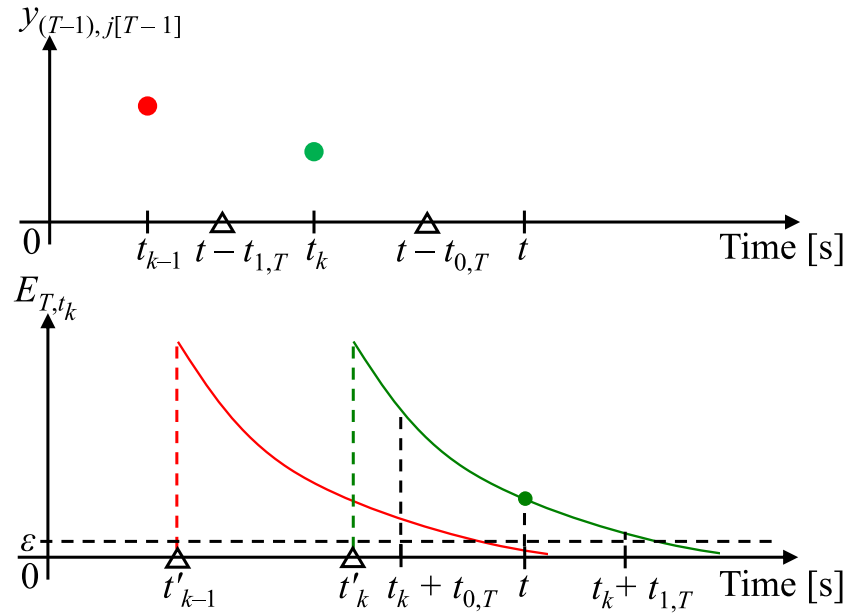


Fig. 3. An example of a CMA measured at different sampling times and its corresponding RTD functions to be used in CMA prediction. The materials that entered the target process at t_k begin to be discharged at t'_k . Only the $E_{T,t_k}(t)$ of curves starting at t'_k and t'_{k+1} will be used in CMA prediction because t is between $t_k + t_{0,T}$ and $t_k + t_{1,T}$, and $t_{k+1} + t_{0,T}$ and $t_{k+1} + t_{1,T}$.

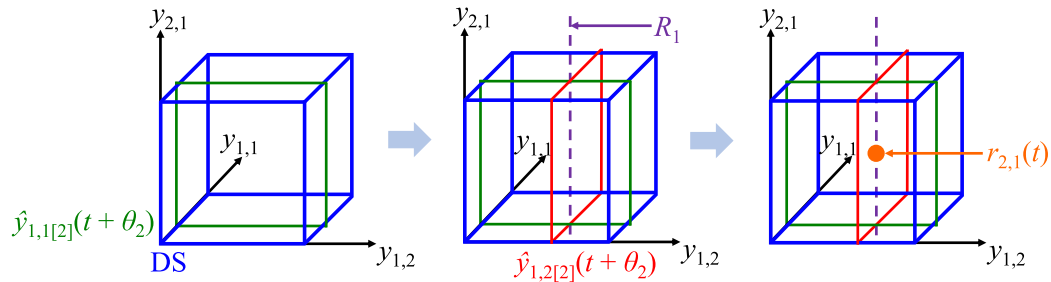


Fig. 4. An example of setpoint determination, where the total number of processes is two, the number of CMAs of process 1, P_1 , is two, the number of CMAs of P_2 is one and the target process is P_2 . The figure on the left shows the hyperplane formed by the first CMA of P_1 predicted at the outlet of P_2 at $t + \theta_2$, $\hat{y}_{1,1[2]}(t + \theta_2)$, where θ_2 is the lag time of P_2 . The figure in the middle demonstrates the hyperplane formed by $\hat{y}_{1,2[2]}(t + \theta_2)$ and the overlapping region of the two hyperplanes, denoted by the dashed line, R_1 . The setpoint is the center of gravity of the vertices of the shared segment between R_1 and the DS. The dot in the figure on the right indicates the setpoint of the first CMA of P_2 , $r_{2,1}(t)$.

By introducing the concept of RDS, the P-RTD method can determine set points flexibly enough to keep CQAs within their acceptable region. Although Fig. 4 illustrates a three-dimensional DS for simplicity, the P-RTD method is applicable to a higher dimensional DS. In addition, even in cases where significant confounding exists among CMAs, the P-RTD method can function effectively as long as the design space is appropriately defined.

Because the DS is a parallelotope, inputs can be transformed into an axis-aligned hyper-box or hyperplane via linear transformations. Overlap calculations in each loop and the final setpoint determination are then easily performed. The total computational cost is $\mathcal{O}(Tn^2)$. Even for large-scale cases (e.g., $n = 10$ and $T = 10$), the entire calculation completes in less than 1 ms on a standard CPU.

2.3. Other methods of setpoint determination

The P-RTD method is compared with three other setpoint determination methods: fixed setpoint method (Fixed SP), mean residence time method (MRT) and RTD method. In the Fixed SP method, the setpoints are fixed at the average of the minimum and maximum values of $y_{i,j}$ in the DS. The MRT, RTD and P-RTD methods share the same setpoint determination algorithm but each method uses CMAs at different times. The MRT method assumes that a material that enters P_T leaves after its

MRT, $t_{m,T}$, which is calculated using the RTD function of P_T , $E_T(t)$, as follows:

$$t_{m,T} = \int_0^\infty t E_T(t) dt \quad (2)$$

The MRT method uses $y_{i[i]}(t - t_{m,T})$ ($i = 1, 2, \dots, T-1$) to determine $r_T(t)$. In the RTD method, $\hat{y}_{i[T]}(t)$ computed from Eq. (1) are used, while the P-RTD method uses $\hat{y}_{i[T]}(t + \theta_T)$.

In industrial practice, dynamic adjustment of setpoint is still not commonly adopted. Therefore, the Fixed SP method would be a representation of the current industrial standard. On the other hand, since the utilization of RTD has been actively discussed in the context of continuous manufacturing, we selected the MRT method and the RTD method as baselines that explicitly incorporate RTD information. These approaches are intuitive and likely among the first methods a practitioner would consider when aiming to utilize RTD.

3. Control simulations

3.1. Processes

Fig. 5 shows the continuous dry granulation line used in simulations, which consists of a continuous paddle mixer, a roller compactor, and a tablet press. This study is not dependent on specific equipment.

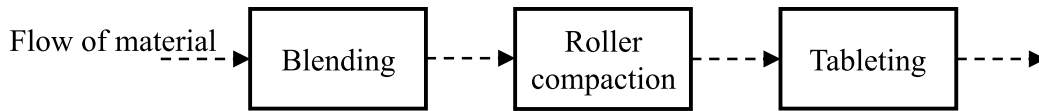


Fig. 5. Continuous dry granulation line with three processes, blending, roller compaction and tableting, used in simulations.

Table 2

CPPs and CMAs of each process used in simulations: blending, roller compaction and tableting.

Process	Symbol	Description	Range	Unit
Blending	$y_{1,1}$	Particle size distribution under 75 μm	6%–58%	–
Roller compaction	$u_{2,1}$	Hydraulic pressure	10–100	MPa
	$y_{2,1}$	Ribbon density	800–1200	kg m^{-3}
Tableting	$u_{3,1}$	Tablet height	3.8–5.0	mm
	$u_{3,2}$	Feed volume	0.9–1.1	cm^3
	$y_{3,1}$	Tablet hardness	314–471	N
	$y_{3,2}$	Tablet mass	0.444–0.466	g

Table 3

Parameters of the RTD function of roller compaction and the tableting processes.

Process	Parameter	Value [s]
Roller compaction	θ_2	161
	τ_2	340
	θ_3	76
Tableting	τ_3	210

It consists of three processes, P_1 : blending, P_2 : roller compaction and P_3 : tableting. The CMA of P_1 is $y_1 = [y_{1,1}] = [\text{particle size distribution under } 75 \mu\text{m}]$. Similarly, $y_2 = [y_{2,1}] = [\text{ribbon density}]$ and $y_3 = [y_{3,1}, y_{3,2}] = [\text{tablet hardness, tablet mass}]$. The CPP of P_2 is $u_2 = [u_{2,1}] = [\text{hydraulic pressure}]$, and CPPs of P_3 are $u_3 = [u_{3,1}, u_{3,2}] = [\text{tablet height, feed volume}]$. Here, tablet height is selected as a CPP, instead of tablet pressure. In general, tablet pressure affects tablet height (density) and then tablet hardness, and both tablet pressure and tablet height are simultaneously changed by adjusting the distance between upper and lower punches. Hence, either tablet height or tablet pressure can be used as a CPP for tablet hardness. CPPs and CMAs used in simulations, along with their respective ranges, are summarized in Table 2. CPPs of the blending process are not mentioned in Table 2 because, in our simulations, variations in P_1 are tolerated, and P_2 and P_3 are controlled. Ranges of $y_{2,1}$ and CPPs and CMAs of the tableting process were obtained based on Singh et al. (2012) and Copot (2022), respectively. Here, tablet hardness was obtained from the values of 4–6 MPa used by Copot (2022) assuming the round tablet diameter is 10 mm. Realistic ranges were chosen for the remaining CMA and CPP.

We utilized single-input single-output control systems: $y_{2,1}$, $y_{3,1}$ and $y_{3,2}$ were controlled by $u_{2,1}$, $u_{3,1}$ and $u_{3,2}$, respectively. Martinetz et al. (2018) showed that a model of a continuous drying granulation line can be expressed using a combination of one PFR and one CSTR. The RTD function of P_i ($i = 2, 3$) is given by the combined model with one PFR and one CSTR:

$$E_i(t) = \begin{cases} 0 & (t < \theta_i) \\ \frac{1}{\tau_i} \exp\left\{-\frac{1}{\tau_i}(t - \theta_i)\right\} & (t \geq \theta_i) \end{cases} \quad (3)$$

where τ_i is a parameter related to the MRT of P_i . Table 3 summarizes the parameters of the RTD functions of the roller compaction and tableting processes. The values of θ_i were presented in the research by Martinetz et al. (2018). Although τ_i values were not presented, we obtained the approximated values from the time responses of the 15 kg h^{-1} mass flow rate in Martinetz et al. (2018). Simulations were also conducted for $2\theta_i$ and $3\theta_i$. The threshold ϵ for RTD functions was set to 1.0×10^{-5} . CMAs are measured at the outlet of each process by PAT at every sampling time. Both t_s and the control interval were set to 1 s.

3.2. PI controller tuning

In the control simulations, multiloop PI control was used, aiming to isolate and highlight the effectiveness of the proposed P-RTD method for setpoint design. This approach allows for a clearer assessment of the impact of setpoint strategies without the confounding complexity of advanced control schemes. The P-RTD method can be applied not only to the multiloop control structure but also to more sophisticated multivariable control systems such as model predictive control (MPC). Thus, the proposed method remains applicable and beneficial even when variable interactions are non-negligible.

The PI control law is expressed using the manipulated variable $u(t)$ and the control error $e(t)$ as follows:

$$u(t) = K_P \{e(t) + \frac{1}{T_I} \int_0^t e(\lambda) d\lambda\} \quad (4)$$

The proportional gain K_P and the integral time T_I were determined based on the SIMC method (Skogestad, 2003). When K_c , T_c and L_c are the gain, time constant and dead time of the process transfer function, K_P and T_I are determined by the following equations:

$$K_P = \frac{T_c}{2K_c L_c}, \quad T_I = \min(T_c, 8L_c) \quad (5)$$

3.3. Design space

This study used a four-dimensional DS defined by the four CMAs in Table 2, where upper and lower bounds were set for tablet mass: $y_{3,2} \in [0.444, 0.466]$. Under this situation, the four setpoint determination methods used in this study always determine $r_{3,2}$ as the average of upper and lower bounds of $y_{3,2}$; thus, a three-dimensional space defined by $y_{i,1}$ ($i = 1, 2, 3$) is sufficient for setpoint determination. Fig. 6 shows the parallelepiped used to determine $r_{i,1}$.

3.4. Variation of CMAs

We prepared $y_{1,1[1]}$ between 6%–58% to assure that it stays within the DS, as depicted in Fig. 7.

Fig. 8 summarizes the factors influencing the variation of CMAs. $y_{2,1}$ is affected by both $u_{2,1}$ and $y_{1,1}$ (Singh et al., 2012). Likewise, $y_{3,1}$ is influenced by $u_{3,1}$ and $y_{2,1}$ (Copot, 2022; Crowley et al., 2017; Singh et al., 2012). $y_{3,2}$ is altered by $u_{3,2}$ and $y_{2,1}$ (Copot, 2022; Singh et al., 2012). Every transfer function is a first-order transfer function with a dead time. Table 4 outlines the parameters of the transfer functions.

Transfer functions from CPPs to CMAs were determined using previous research (Copot, 2022; Singh et al., 2012). When a transfer function was given as a second-order process, it was converted to a first-order transfer function using the half rule as proposed by Skogestad (2003).

On the other hand, there are no prior studies that explicitly defined transfer functions between CMAs. Thus, transfer functions between CMAs were determined based on the characteristics of CMAs. When particles are smaller in size, they can pack more closely together when compressed. This results in a higher density of particles within the ribbon. Therefore, a positive gain was set to the transfer function from $y_{1,1}$ to $y_{2,1}$. Acevedo et al. (2012) and Teng et al. (2009) mentioned that high ribbon densities may result in lower tablet hardness. Thus, a negative gain was set to the transfer function from $y_{2,1}$ to $y_{3,1}$. A positive value was set for the gain of the transfer function from $y_{2,1}$ to $y_{3,2}$ because tablet mass increases with the increase of ribbon density at constant feed volume, which is observed in realistic processes. We

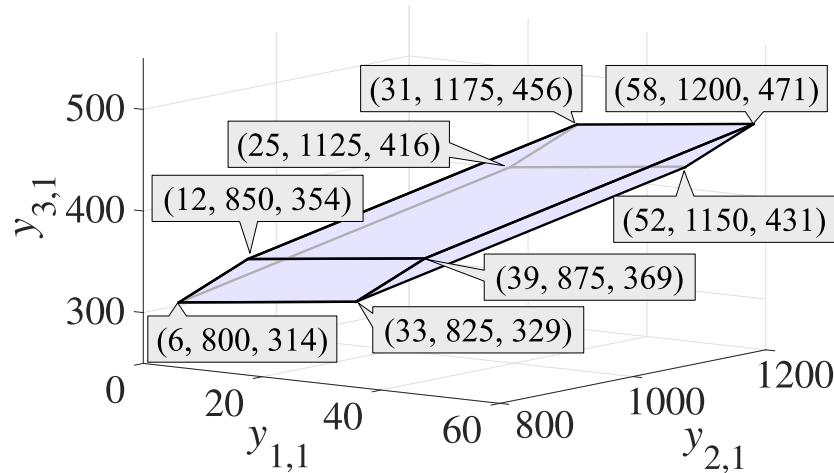


Fig. 6. Parallelepiped used to determine setpoints. First, second and third coordinates of vertices correspond to $y_{1,1}$, $y_{2,1}$ and $y_{3,1}$, respectively.

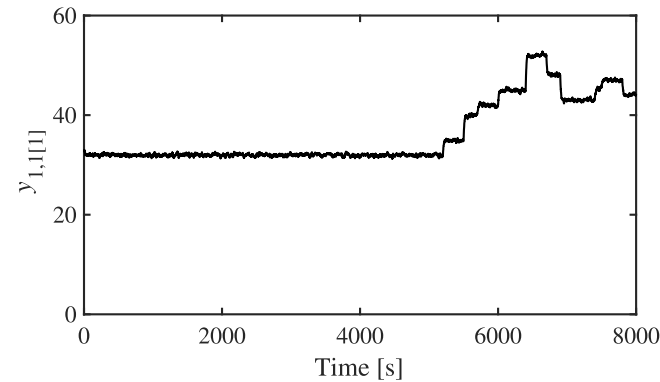


Fig. 7. Data of particle size distribution under $75\mu\text{m}$ [%], which is the CMA at the outlet of process 1, used in all simulations.

Table 4
Parameters of transfer functions. T_c and L_c represent time constant and dead time.

Input	Output	Gain	Unit of gain	T_c [s]	L_c [s]
$u_{2,1}$	$y_{2,1}$	31.25	$\text{kg m}^{-3} \text{MPa}^{-1}$	15	20
$u_{3,1}$	$y_{3,1}$	-408.407	N mm^{-1}	14.8	25.54
$u_{3,2}$	$y_{3,2}$	0.4757	g cm^{-3}	6.58	18.63
$y_{1,1}$	$y_{2,1}$	0.7, 0.9	kg m^{-3}	30	322
$y_{2,1}$	$y_{3,1}$	-0.59, -0.69	$\text{N kg}^{-1} \text{m}^3$	50	152
$y_{2,1}$	$y_{3,2}$	4×10^{-5} , 1.2×10^{-4}	$\text{g kg}^{-1} \text{m}^3$	40	152

Table 5
Combinations of process gains from CMAs to CMAs.

Case	$y_{1,1}$ to $y_{2,1}$ [kg m^{-3}]	$y_{2,1}$ to $y_{3,1}$ [$\text{N kg}^{-1} \text{m}^3$]	$y_{2,1}$ to $y_{3,2}$ [$\text{g kg}^{-1} \text{m}^3$]
1	0.7	-0.59	4.0×10^{-5}
2	0.7	-0.59	1.2×10^{-4}
3	0.7	-0.69	4.0×10^{-5}
4	0.7	-0.69	1.2×10^{-4}
5	0.9	-0.59	4.0×10^{-5}
6	0.9	-0.59	1.2×10^{-4}
7	0.9	-0.69	4.0×10^{-5}
8	0.9	-0.69	1.2×10^{-4}

set two different gains for transfer functions from CMAs to CMAs. Simulations were carried out for 8 different gain combinations, which are summarized in Table 5. The process gains were adjusted so that the simulation results would align with the knowledge and experience of practitioners through the sensitivity analysis.

Table 6
Duration spent outside of the DS (T_{out}) during 3000 s with the four methods in different combinations of process gains from CMAs to CMAs.

Case	1	2	3	4	5	6	7	8
Fixed SP	1149	1149	1149	1149	1149	1149	1149	1149
MRT	565	565	610	610	563	563	607	607
RTD	55	55	111	111	53	53	110	110
P-RTD	0	0	0	0	0	0	0	0

The total simulation time was 8000s, and the first 5000s were excluded in evaluations to avoid the influence of the initial values of CMAs.

4. Results and discussion

We evaluated the duration at least one $y_{i,j[3]}$ ($i = 1, 2, 3$) fell outside the DS. This duration is termed as T_{out} . Table 6 summarizes T_{out} of each method in 8 cases. Across all cases, the P-RTD method was the only method to attain $T_{\text{out}} = 0$. The P-RTD method is superior to other methods in keeping CMAs within the DS. After further analysis, it was observed that the RTD method failed to sustain the CMAs within the DS during $t = 5749\text{--}5785$ s and $6290\text{--}6362$ s in Case 8. Fig. 9 illustrates the setpoints determined by RTD and P-RTD methods during $t = 6290\text{--}6362$ s in Case 8. It is evident that the setpoints are different. The reason for this difference lies in using CMAs at different times as described in Section 2.3. The P-RTD method uses future values calculated using the RTD function of the target process to determine setpoints and suppresses the effect of dead times of processes.

Table 7 summarizes the mean squared errors (MSEs) of CMAs in Case 8 scaled by the range of $y_{i,j}$ in the DS. The P-RTD method is not the method with the smallest MSEs of CMAs. MSEs of CMAs serve only as a measure of the control performance in reaching the determined setpoints. They do not reflect on the ability of a method to sustain the CMAs within the DS. The P-RTD method uses a better way of determining setpoints and sustains the CMAs within the DS even though it does not have the smallest MSEs of CMAs. The MRT method has the largest MSEs of CMAs. It assumes that a material that entered a process leaves the process after t_m . As a result, the measured CMAs used by the MRT method to determine setpoints differ from the predicted CMAs at outlets of processes. Fig. 10 depicts predicted and measured CMAs in Case 8. It is apparent that the predicted CMAs exhibit smooth fluctuations, while the measured CMAs show rough fluctuations. Thus, setpoints determined by these measured CMAs give larger MSEs of $y_{3,1}$ and $y_{3,2}$.

The relatively low MSE observed for the Fixed SP strategy is primarily due to the absence of setpoint changes. In contrast, the P-RTD

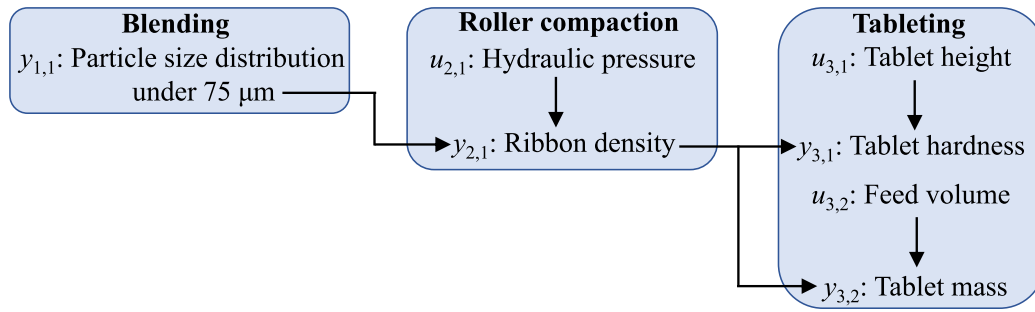


Fig. 8. Causal relationships from CPPs (vertical arrows) and CMAs (horizontal arrows) to CMAs.

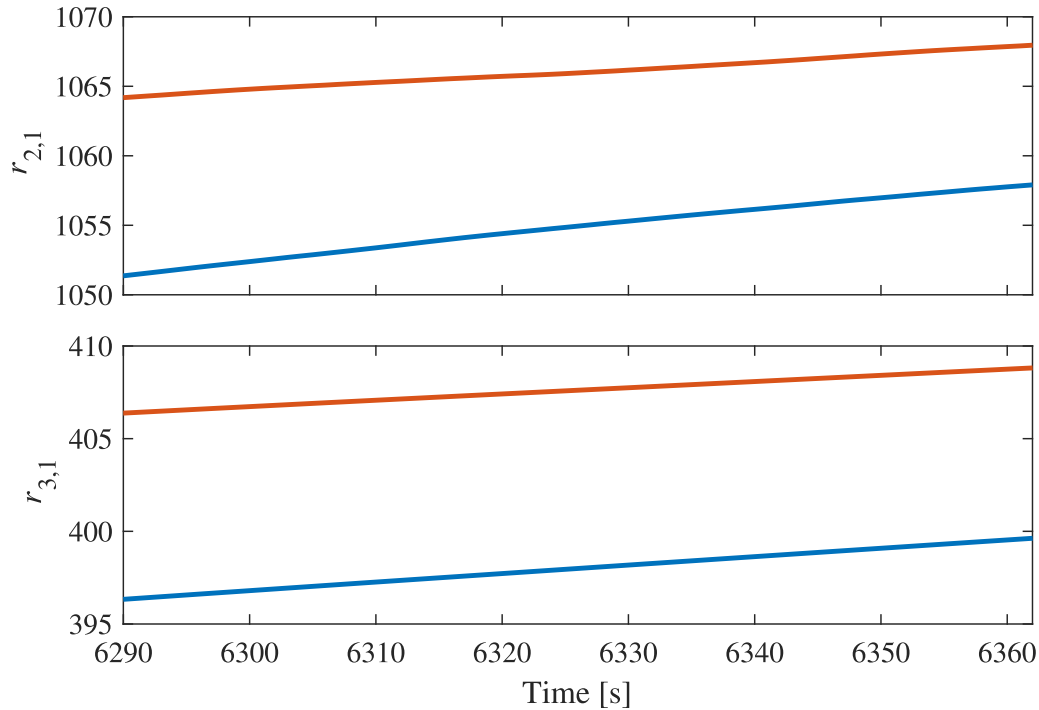


Fig. 9. Comparison of setpoints determined by RTD and P-RTD methods during $t = 6290\text{--}6362$ s in Case 8. Blue lines represent the RTD method, and red lines represent the P-RTD method.

Table 7

Mean squared errors (MSEs) of CMAs in Case 8 scaled by the range of $y_{i,j}$ in the DS ($\times 10^{-4}$).

Method	$y_{2,1}$	$y_{3,1}$	$y_{3,2}$
Fixed SP	17.07	6.608	0.0012
MRT	3394	3877	0.3361
RTD	848.9	1491	0.1124
P-RTD	864.7	1462	0.1147

method and the other RTD-based methods necessarily involve setpoint changes, which lead to transient deviations immediately after each change, thereby increasing the MSE. The similarity in MSE between RTD and P-RTD reflects the fact that both methods utilize RTD to determine setpoints, and thus their profiles exhibit comparable dynamic behavior. Although MSE is a conventional and important performance index in control, the primary goal of this study is to minimize T_{out} , which is a more critical indicator of product quality and process safety.

Fig. 11 illustrates control simulation results of CPPs and CMAs with the four methods in Case 8. $u_{i,j}$ and $y_{i,j[i]}$ with $r_{i,j}$ of each method are plotted against time. Regions shaded in gray denote the times when $y_{i,j[3]}$ fell outside the DS. In the Fixed SP method, the measured CMAs closely follow the setpoints. However, the Fixed SP

method compromises the adaptability to changes in the system such as disturbances and causes $y_{i,j[3]}$ to fall outside the DS. CPPs of the MRT method show rough fluctuations. As depicted in Fig. 10, fluctuation of measured values used to determine setpoints in the MRT method causes fluctuations of calculated setpoints and CPPs.

We also conducted simulations for $2\theta_i$ and $3\theta_i$ ($i = 2, 3$). Tables 8 and 9 outline T_{out} with $2\theta_i$ and $3\theta_i$, respectively. The P-RTD method could achieve $T_{\text{out}} = 0$ in every case for both $2\theta_i$ and $3\theta_i$. Since it takes more than the dead time for the effects of CPPs to appear in CMAs, it is preferred to use predicted values more than the dead time later when determining the setpoints. In this study, the P-RTD method used $y_{i,1[3]}(t + \theta_3)$, which satisfied the above condition, and thereby achieved the best performance. Even when lag times were three times longer, the P-RTD method retained CMAs within the DS for the entire simulation time. These results prove that the P-RTD method is suitable for manufacturing lines consisting of processes with long lag times.

5. Conclusion

The performance of the proposed P-RTD method, a setpoint determination method for CMAs, was tested in realistic continuous dry granulation lines with varying relationships among CMAs and lag times of processes. The P-RTD method consists of two major steps:

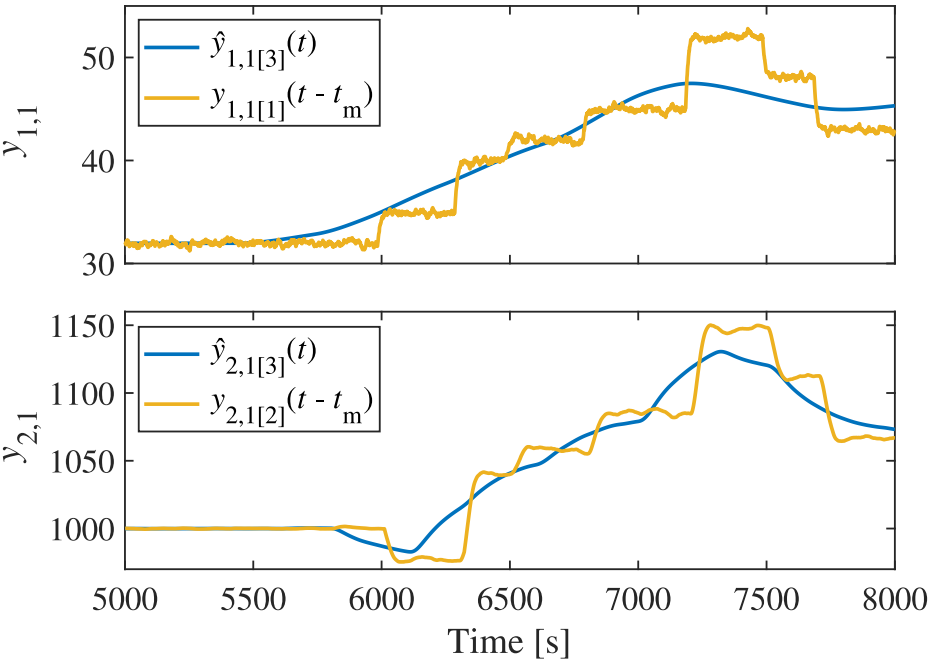


Fig. 10. Comparison of CMA measurements at the outlets of processes 1 and 2, P_1 and P_2 , and predicted at the outlet of P_3 in Case 8.

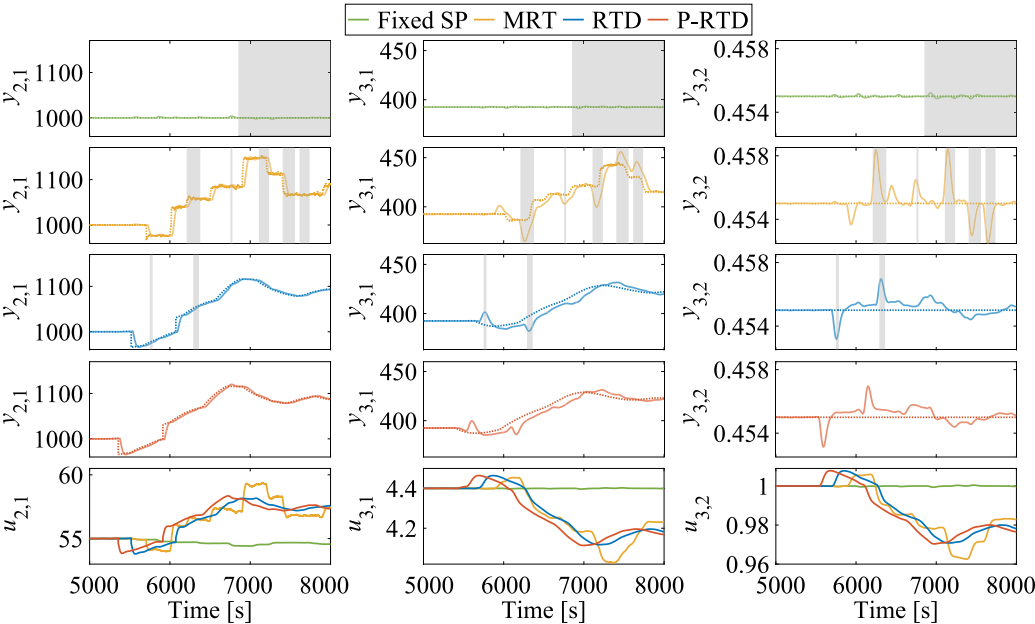


Fig. 11. Control simulation results of CPPs and CMA with the four methods in Case 8. Solid lines represent measured values, and dotted lines represent setpoints. Regions shaded in gray denote the times when CMA fell outside the DS at the outlet of process 3, P_3 . $u_{2,1}$: First critical process parameter of P_2 , $y_{2,1}$: First critical material attribute of P_2 . The quantitative results are summarized in Tables 6 and 7.

Table 8								
Duration spent outside of the DS (T_{out}) during 3000s with $2\theta_i$.								
Case	1	2	3	4	5	6	7	8
Fixed SP	910	910	910	910	910	910	909	909
MRT	715	715	746	746	712	712	744	744
RTD	81	81	125	125	81	81	126	126
P-RTD	0	0	0	0	0	0	0	0

Table 9								
Duration spent outside of the DS (T_{out}) during 3000s with $3\theta_i$.								
Case	1	2	3	4	5	6	7	8
Fixed SP	678	678	679	679	679	679	679	679
MRT	508	508	559	559	509	509	557	557
RTD	26	26	73	73	26	26	73	73
P-RTD	0	0	0	0	0	0	0	0

CMA prediction using RTD functions and setpoint determination in the DS. The simulation results also showed that the P-RTD method succeeded in retaining the CMA within the DS better than the other

methods; the Fixed SP method, MRT method and RTD method. The P-RTD method will contribute to quality assurance in pharmaceutical continuous manufacturing and reduce the wastage of raw materials.

At this stage, the proposed P-RTD method has not yet been validated in actual continuous manufacturing environments; we will apply it to a real process and test its practical effectiveness in future.

CRedit authorship contribution statement

Pasindu Herath Pathirannahalage: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Ayumu Nabetani:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Shota Kato:** Writing – review & editing, Validation, Methodology. **Kanta Sato:** Writing – review & editing, Validation, Methodology, Investigation. **Keita Yaginuma:** Writing – review & editing, Validation, Methodology, Investigation. **Shuichi Tanabe:** Writing – review & editing, Validation, Methodology, Investigation. **Manabu Kano:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Manabu Kano reports financial support was provided by Japan Society for the Promotion of Science (JSPS). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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