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Resilience and risk analysis of fault-tolerant control design in continuous pharmaceutical manufacturing

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Abstract

The effects of the paradigm shift from batch to continuous manufacturing on pharmaceutical industry, in terms of process safety and product quality, *e.g.*, danger of dust explosions and risk of off-spec products, are of major concerns in the recent research progress in control system design. Specifically, a fault-tolerant control of critical process parameters (CPPs) and critical quality attributes (CQAs) is of paramount importance for the continuous operation with built-in safety and quality. In this study, a systematic framework for fault-tolerant control design, analysis, and evaluation for continuous pharmaceutical solid-dosage manufacturing is proposed, consisting of system identification, control design and analysis (controllability, stability, resilience, *etc*.), hierarchical three-layer control structures (model predictive control, state estimation, data reconciliation, *etc*.), risk mapping, assessment and planning (Risk MAP) strategies, and control performance evaluation. The key idea of the proposed framework is to identify the potential risks in the control design, material variance, and process uncertainties, under which the control strategies are evaluated. The framework is applied to a continuous direct compaction process, specifically the feeding-blending system wherein the major source of variance in the process operation and product quality arises. It can be demonstrated that the process operation failures and product quality variances in the feeding-blending system can be mitigated and managed through the proposed systematic fault-tolerant control system design and risk analysis framework.

Introduction

The pharmaceutical industries are undergoing a mindset change from batch to continuous manufacturing, which is convinced by the overwhelming advantages researched in the past decade [1, 2], mostly at the conceptual or modular level. To develop a practically integrated operating pilot plant or manufacturing process [3], efforts from regulators, academics, and industry are now focused more on the plant-wide control system design and operation issues [1, 4], for example, the

process control design and its risk analysis for real-time release in continuous solid-dosage manufacturing.

The continuous solid-dosage manufacturing usually involves unit operations with powders, *i.e.*, feeding, blending, granulation, tableting, *etc*., in which process dynamics due to physical changes of mixing or stress usually occur within seconds or minutes. There is also a limited hold-up in each unit operation and thus the buffering provided by material inventory is limited. Additionally, stream recycling or substantial back mixing in the process must be avoided in the highly-regulated pharmaceutical secondary manufacturing process due to the necessities of material tracking [2]. Therefore, aggressive control responses are often required to address process disturbances, posing the dust-generated manufacturing process threatening [5]. Furthermore, variability in raw materials upstream also has a rapid and direct impact on downstream processes, which affects the in-process materials and final drug product qualities, making the consistent production of quality solid dosage challenging. To this end, a resilient and fault-tolerant plant-wide control system design is critically important to the safety and success of pharmaceutical continuous manufacturing. These features provide the motivation for a systematic framework for process control design and risk analysis in continuous manufacturing processes [6, 7].

This manuscript is organized as follows. First, the proposed systematic framework for resilient fault-tolerant control design and risk analysis will be defined, followed by the introduction to a continuous feeding-blending system, used as the illustrative case study. The application of the systematic framework to the feeding-blending system will be discussed in the Results and Discussion section. Finally, concluding remarks on the application of the systematic framework will be presented.

Resilient fault-tolerant control design and risk analysis

The proposed systematic framework is generic and in principle can be applied for the design and analysis of control systems for any pharmaceutical continuous manufacturing process, as shown in Figure 1.

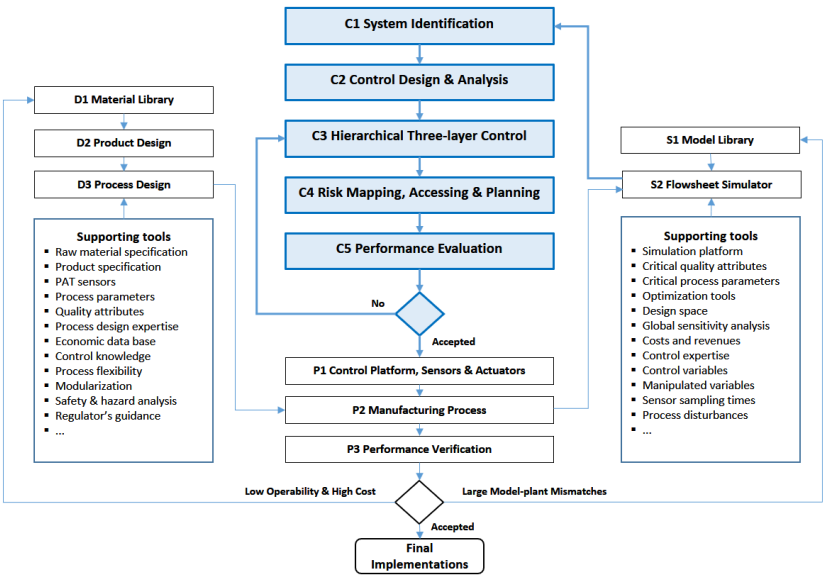

Figure 1. Systematic framework for process control design & risk analysis

The framework interfaces with additional supporting knowledge and tools that facilitate the integration of software and hardware for control strategy design and implementation. After proper Product Design (D2) based on the knowledge drawn from the Material Library (D1), an appropriate formulation for the solid dosage will be generated, requiring a specific continuous manufacturing technology in the Process Design (D3). A pilot plant or Manufacturing Process (P2) will then be configured using modularized unit operations (feeding, blending, tableting, *etc*.) provided by equipment vendors with associated integration of control platform and PAT sensors in the P1 development step. Process modeling tools consisting of a Model Library (S1) and Flowsheet Simulation (S2) software play an important role in efficient plant-wide control strategy development by accelerating process design optimization and achieving desired control objectives. For example, global sensitivity analysis and System Identification (C1) based on Flowsheet Simulation (S2) can help to identify and address the potential challenges or risks in process control design, *i.e.*, decentralization, pairing, stability, resilience, *etc*., through rationale control design metrics in the Control Design & Analysis (C2), as shown in Figure 2. A hierarchical three-layer process control design (C3) and risk analysis (C4) will be followed with rigorous performance evaluation (C5), as shown in Figures 3 and 4. Specifically, the hierarchical control structure is focused more on the implementation with the layers classified according to the scale of their control objectives, the process understanding needed and the potential capabilities in handling process disturbances and risks. Herein, a risk map for the manufacturing process can be presented as a matrix to characterize the likelihood that a risk event will occur and its impact on the production. Only the nominal risks that are acceptable to the continuous manufacturing are investigated. The acceptable risk scenarios identified from the risk mapping, are further ranked into three categories according to their frequency and severity: R0 low risk, R1 medium risk, and R2 high risk. Iterations between steps C3 to C5 will continue until a controller design, which meets real-time release requirements and, adheres to regulatory guidance are achieved. The resulting control design will then be implemented on the Manufacturing Process (P2) and verified experimentally in step P3. Continuous improvements of the manufacturing process (P2) will be pursued either by improving the model prediction accuracy or by enhancing the product and process designs (D1 & D2).

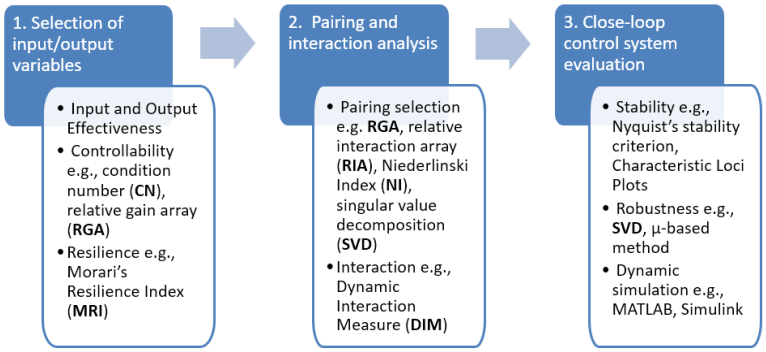

Figure 2. Three-step procedure for control design and interaction analysis

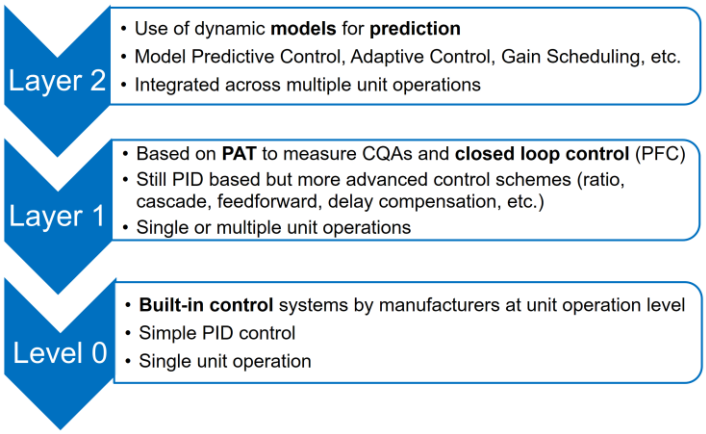

Figure 3. General three-layer classification of control approaches

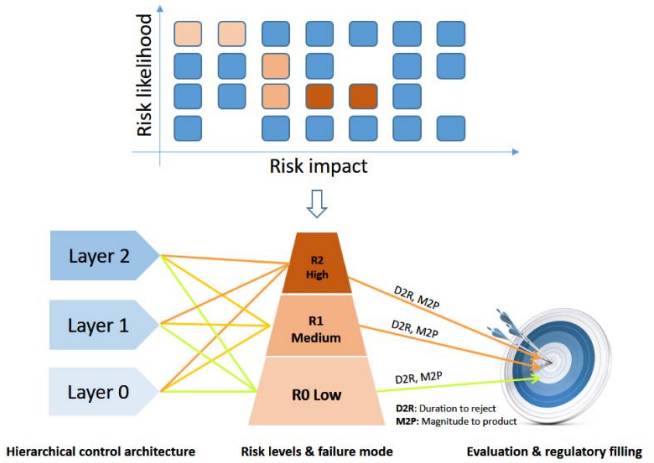

Figure 4. Framework for risk-based feedback control evaluation

Results and discussion

A continuous feeding-blending system

Continuous blending is the first step in continuous solid-dosage manufacturing, wherein API content and its uniformity in the powder are the two important CQAs that must be strictly controlled in this subsystem. In this study, the proposed framework was applied to a continuous feeding-blending system. It consists of two Schenck AccuRate PureFeed® AP-300 loss-in-weight feeders that are capable of achieving and maintaining specified feed rates by measuring and using the changes in remaining powder weight in the combined hopper and feeder unit. This is achieved through an imbedded Layer 0 control system. The feeders continuously feed the API, Acetaminophen (APAP), and the excipient, Avicel Microcrystalline Cellulose PH-200 (MCC 200), into a Gericke GCM-500 continuous blender, wherein the two components mixed. The nominal operating conditions (NOC) consist of API flow of 1.0 kg/h, and excipient flow of 9.0 kg/h, and the blender rotation speed of 200 rpm. The API mass fraction was measured *in situ* using a Near Infrared spectrometer (Control Development, Inc.) at the exit of the blender [8, 9]. The content uniformity was statistically estimated in the form of relative standard deviation (RSD) using mean and variance of the API mass fraction measurements within a time window [10]. The powder flow is measured using an X-ray based mass flow meter (SETXvue XP-300, Enurga, Inc.) [11]. These

pieces of equipment are integrated and their process variables were transmitted to the Emersion DeltaV system. An OPC DA protocol through LinkMaster and KepServer packages was also established to transmit real-time process data from Emerson DeltaV OPC server to MATLAB, where the data is accessed by the Layer 2, as shown in Figure 3.

A flowsheet model was developed for the feeding-blending system in SIMULINK. The two loss-in-weight feeders were modeled using the first-order plus-time-delay (FOPTD) transfer functions and were both controlled in Layer 0 using proportional-integral-derivative (PID) controllers to adjust the screw rotation speed. The PID gains for Layer 0 control were automatically tuned with SIMULINK control design. The continuous blender was modeled with a two-dimensional compartmental model, with fluxes estimated for each component in forward, backward, and radial directions. The blender rotation speed was also controlled at Layer 0 by manipulating the motor current. The other process variables for Layer 1 and 2 control designs are given in Table 1.

Table 1. The feeder-blender control system

Unit operation	**Process output (y)**	**Process input (u)**	**Control Layer**	**Controller type**
API feeder	API flowrate	Screw rotation speed	L0	PID
Exp. feeder	Exp. flowrate	Screw rotation speed	L0	PID
Blender	API composition	API flowrate	L1/2	PID, Ratio, MPC
	Powder flowrate	Excipient flowrate	L1/2	PID, MPC
	API mixing RSD	Rotation speed	L1/2	PID, MPC
	Rotation speed	Motor current	L0	PID

Control design and analysis

For system identification, random step changes to the process input (**u**) are introduced in the SIMULINK flowsheet model to collect the process dynamic data. A system transfer function matrix **G** was then identified using the MATLAB system identification toolbox in the form of a state-space model. With the system matrix **G**, control design and analysis metrics were then applied, as shown in Figure 2.

A condition number of 3.2945 (< 25) and a Morari's Resilience Index of 0.4372 show that the feeding-blending system is controllable and stable at the current nominal operating condition even with a decentralized control scheme at Layer 1. And the Niederlinski Index of 1.10 (>0), the relative gain array (RGA), and the relative interaction analysis (RIA) pairing metrics all indicate that a stable design is achieved by a diagonal pairing under which the API composition is controlled by manipulating the API feeding flowrate, the blender powder flowrate by the excipient feeding flowrate, and the API mixing RSD by the blender rotation speed, as shown below.

$$RGA = \begin{bmatrix} \mathbf{0.9008} & 0.0999 & -0.0007 \\ 0.0944 & \mathbf{0.9058} & -0.0002 \\ 0.0048 & -0.0057 & \mathbf{1.0009} \end{bmatrix} \quad (1)$$

$$RIA = \begin{bmatrix} \mathbf{0.1101} & 9.0131 & -1405.4 \\ 9.5942 & \mathbf{0.1040} & -5371.2 \\ 208.81 & -177.54 & \mathbf{-0.0009} \end{bmatrix} \quad (2)$$

Furthermore, for the chosen diagonal pairing at Layer 1 control, the dynamic interaction measure (DIM) of 40.50 > 15 and the diagonal DIM of 60.25 >15 both suggested that compensation is needed to reduce the interaction, and the μ interaction measure of 2.667 >1 also indicated that the decentralized controllers at Layer 1 may not be stable in closed loop. Furthermore, the performance interaction measure (PIM) of 2.00 = 2 suggests that there is considerable performance interaction in the system. To address these features, a Layer 1 design with decentralized SISO PID control loops, which are compensated by a feedforward ratio controller and a Layer 2 design with linear MIMO model predictive control (MPC) for the feeding-blending system were implemented and tested. A benchmark Layer 0 control design is also included for comparison purpose.

Control performance evaluation

Three risk scenarios arising from common cause errors in the feeding-blending system were identified as acceptable risks and were considered in this study for evaluating the performance of the above control designs.

First, when the loss-in-weight feeder is under reloading [10], a short period of disturbance in feeding can arise, which is considered to be a R0 risk, viz., a measurable disturbance. Herein, a R0 risk scenario consisting of a pulse disturbance to both API and excipient feeders was imposed on the feeding-blending system from the simulation time of 60 s to 90 s as shown in Figure 5, during which the API feeding flowrate was reduced by 15% and the excipient flowrate was increased by 15%. Secondly, the vibrations in the feeder produced by the screw rotation could considerably disturb the load cell measurement, which may lead to a calibration error in the feed flowrate. This was regarded as a R1 risk in this study. A risk scenario of R1 was assumed to occur with the feeders from simulation time of 500 to 1500 s, during which time measurement errors of up to -25% and 25% were introduced to the API and excipient feeders, respectively. The third risk scenario, a higher, level R2 risk, assumed that under the occurrence of calibration errors of R1, the API component also suffered a reduced mixing uniformity in the blender due to, perhaps powder cohesion, and the flux flow in the radial direction was decreased by 8.0% from the simulation time of 1000 to 1500 s in Figure 5.

It is observed that L0 control was capable of tackling the R0 measurable disturbance in the feeders. However, it failed to respond to risk scenarios R1 and R2. The API mean composition fell below the desired 10% set point from 500 s due to the R1 risk and the mixing uniformity variation increased to the upper limit of 6% after 1000 s when the R2 risk occurred. On the other hand, both the L1 and L2 controls were able to handle all the three risk scenarios. This was because any deviations in the CQA's from their desired set points could be detected by the PAT tools and corrected using feedback control. When it comes to the comparative performance of L1 and L2, the MPC advanced control technique used in L2 provided only slight improvement. The model-plant mismatch under the R1 and R2 risks could lead to the less promising performance of the Layer 2 MPC control.

Gross errors or signal drift due to probe fouling are detrimental to most of the PAT tools that are based on spectroscopy and associated calibration models [12], which are also categorized as

an R2 risk. To illustrate this situation, the NIR probe for API composition measurement was considered to have drifted in the time interval from 40 to 100 seconds and to have suffered a gross error of 20% from 100 to 240 seconds before it was detected and corrected, as shown in Figure 6 for Layer 0 control. In this case the NIR probe was only used for API composition monitoring and not integrated within any feedback control loop. In Layer 1 control, the faulty measurement was incorporated into the feedback control loop and was observed as a deviation in the API mean composition and blend uniformity from their set points before the failure in the NIR measurement was detected and corrected. The Layer 2 control, which employs a robust Kalman state estimator with a data reconciliation matrix, could reject the measurement gross error when large model-plant mismatches were detected. In this case, as shown in the bottom three figures of Figure 6, the Layer 2 control was still able to continue the control actions with a predicted API composition.

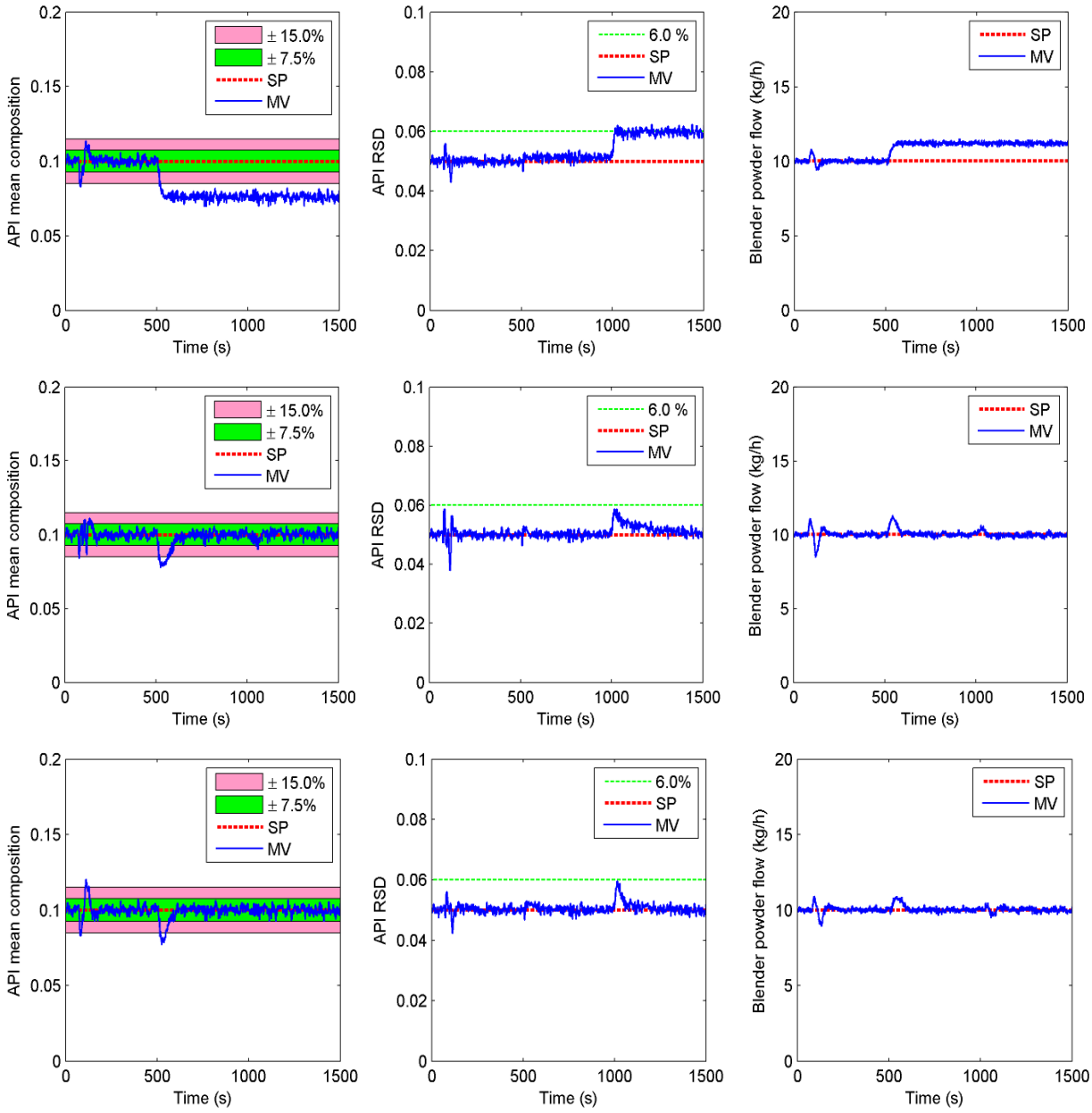

Figure 5. Control performances of different control Layers under risk scenarios (top three: Layer 0 control; center three: Layer 1 control; bottom three: Layer 2 control)

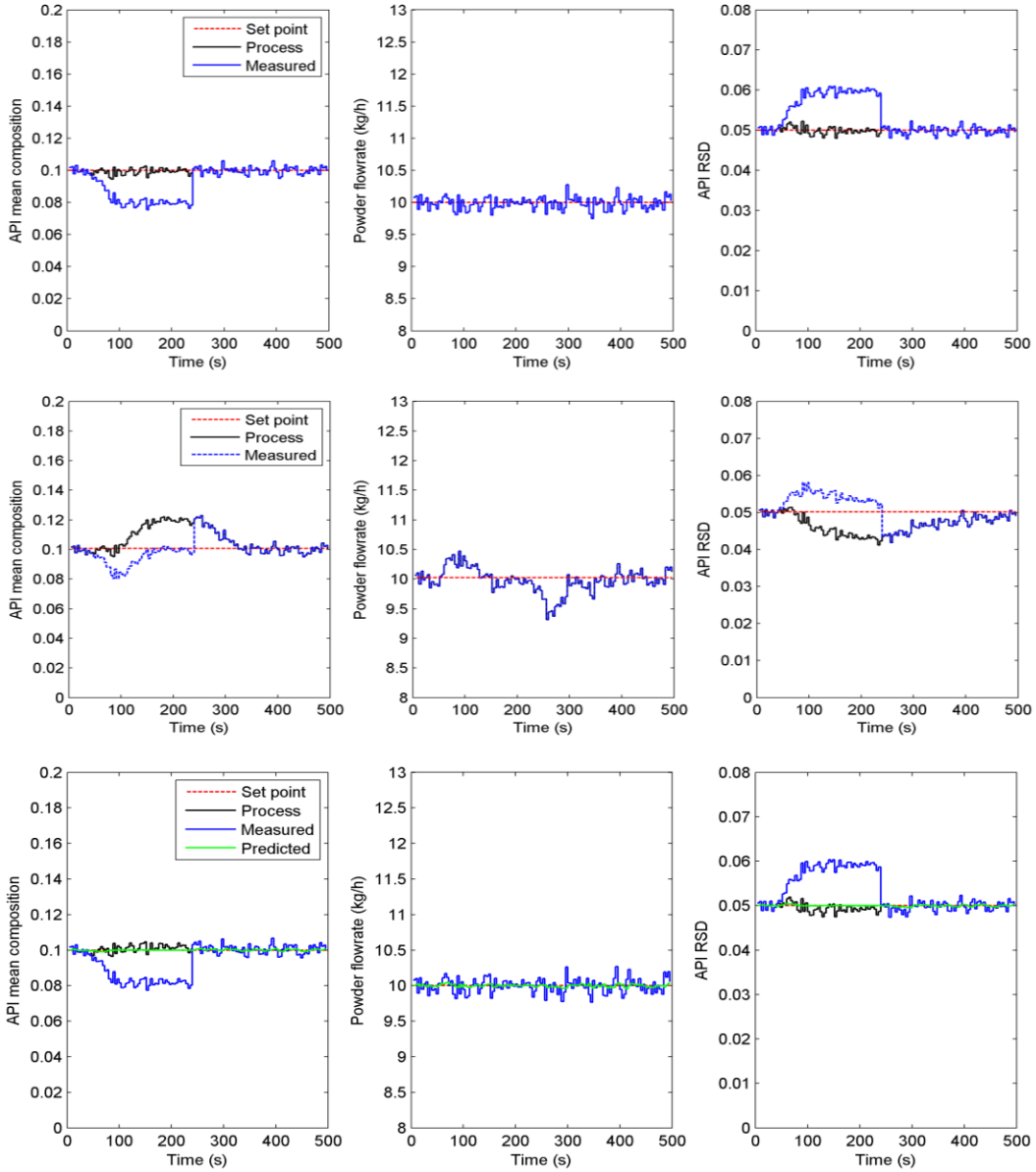

Figure 6. Control performance when R2 PAT gross error occurs to API composition measurement (top three: Layer 0 control; center three: Layer 1 control; bottom three: Layer 2 control)

Conclusions

A systematic framework for a fault-tolerant control system design in continuous manufacturing processes has been proposed to evaluate each step of the control system development with resilience and risk analysis. The proposed hierarchical three-layer control design approach has been applied to a feeding-blending system using a SIMULINK dynamic process model. Based on the risk MAP design, potential risks under which the control performance may deteriorate were also taken into account in evaluating the three-layer control design. These case studies demonstrate the importance of a systematic control evaluation system to assure product quality in continuous manufacturing processes.

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