CONDITION-BASED MAINTENANCE FOR SENSOR NETWORK ROBUSTNESS IN CONTINUOUS PHARMACEUTICAL MANUFACTURING

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Abstract Overview

Quality-by-Design (QbD) and continuous manufacturing (CM) in the pharmaceutical industry have advanced from technology development to adoption for multiple products and processes over the past decade. However, challenges in process analyzer systems during operations such as real-time data handling, sensor positioning, sampling, fouling, etc. can result in data loss, measurement drifts and affect process data accuracy, thereby potentially leading to systemic failures of the process. This work focuses on leveraging process systems engineering methods to mitigate sensor failures and pursue operational excellence in drug product CM. An integrated data-driven and model-based framework for robust process monitoring and systematic maintenance management are configured and demonstrated in a continuous tableting pilot plant at Purdue University. An analytically redundant sensor network using equipment sensors and process analyzers is configured and networked using automation systems for supervisory process control. A maintenance action is configured based on observed process conditions. The pilot plant studies are leveraged for modules in a graduate course on Smart Manufacturing.

Keywords

Pharmaceutical Manufacturing, Process Monitoring, Maintenance Management, Systems Integration.

Introduction

Since the mid-2000s, the Quality by Design (QbD) and Process Analytical Technology (PAT) guidelines by the United States Food & Drug Administration (FDA) have promoted a culture of science and risk-based approach to pharmaceutical development and manufacturing, with an aim to provide high quality and affordable medication and to mitigate drug shortages. Continuous manufacturing (CM) of drug products is one of the key innovations in this modernization.

At its core, CM envisions an intensification of manufacturing processes and supply chains with the systematic integration of product and process knowledge, instrumentation and automation systems, quality control protocols and real-time process management strategies in a highly regulated industry for the real-time release of drug products. With the increased acceptance of CM to benefit business needs, the community now pursues the operational excellence of the manufacturing system.

Instrumentation systems for product quality and process health monitoring in real-time are the foundational requirement for CM and real-time release. Process performance and product quality are obtained using direct measurements and soft sensors (Almaya, et al., 2017, Su et al., 2019). However, challenges in the implementation of these systems, as shown in Fig. 1, could result in measurement gross errors such as drifts, bias, or loss of data, and hence potentially cause a systemic failure of such continuous processes.

The advent of Industry 4.0 or Smart Manufacturing in the 2010s, as a manifestation of cultural and mindset change, is resulting in utilizing highly networked, automated and data-rich systems to realize lean

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manufacturing in multiple industries. These technologies leverage cross-industry advances in manufacturing methods, automation, data analytics, fault management, and implementation technologies, etc. for sustainable process operations, safety, quality risk assessment, and enhanced customer relations.

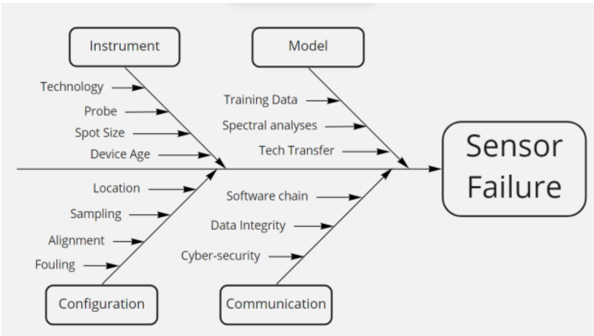

Figure 1: Potential failure sources of process analyzers

This work focuses on leveraging these systems engineering methods for real-time operations management, in particular, condition-based maintenance to improve operational reliability by mitigating sensor network failures in drug product CM. We will discuss the following: (i) an integrated data-driven and model-based framework for systematic sensor network fault monitoring, (ii) the configuration and implementation of condition-based maintenance in a tablet processing pilot plant at Purdue University, and (iii) utilizing the pilot plant studies in chemical engineering graduate courses.

Process description

The continuous tablet manufacturing serially integrates relevant solids processing unit operations, such as screw feeders, granulators, mills and compaction systems. The experimental facility at Purdue University is comprised of 4 loss-in-weight feeders, two blenders, a dry granulation system, and a rotary tablet press. In-line instrumentation systems and equipment sensors are utilized for monitoring critical process variables such as mass flow, composition, tablet weight, dimension and hardness, etc. In this work, we utilize a continuous direct compression process comprising of 3 LIW feeders, two blenders, and a tablet press to configure and demonstrate the maintenance management framework.

Systems integration

A hierarchical systems integration architecture is established for real-time operational decisions in the implementation of Quality-by-Design in continuous pharmaceutical manufacturing based on ISA-95 and Smart Manufacturing architectures (Lopez et al., 2018).

The architecture uses DeltaV 13.3 (Emerson) as the distributed control system to integrate data from equipment and inline process analyzers using suitable communication protocols to track the continuous process. The PI System (OSIsoft) is implemented as the data integrator and historian for harmonizing data from the process, validation of sensors, and the characterization lab. The PI Asset Framework (PI AF) is utilized for standardizing asset templates and support additional analyses. PI AF data is used in SmartFactory Rx (Applied Materials) for workflow-based analyses for fault diagnosis and strategizing maintenance decisions. Matlab (MathWorks) is utilized to support additional analysis. Finally, a repository of the process data is extracted using PI DataLink in Excel, and the configured experimental setup information are recorded as instances in a customized workflow on a HubZero based Knowledge Provenance and Management System (Joglekar 2014) for further knowledge management and education.

Sensor Network Maintenance

In continuous tablet manufacturing, four leading causes of instrumentation faults are observed, which affect monitoring robustness. These include communication failure, instrument configuration, calibration and instrument age, as shown in Figure 1. Monitoring the

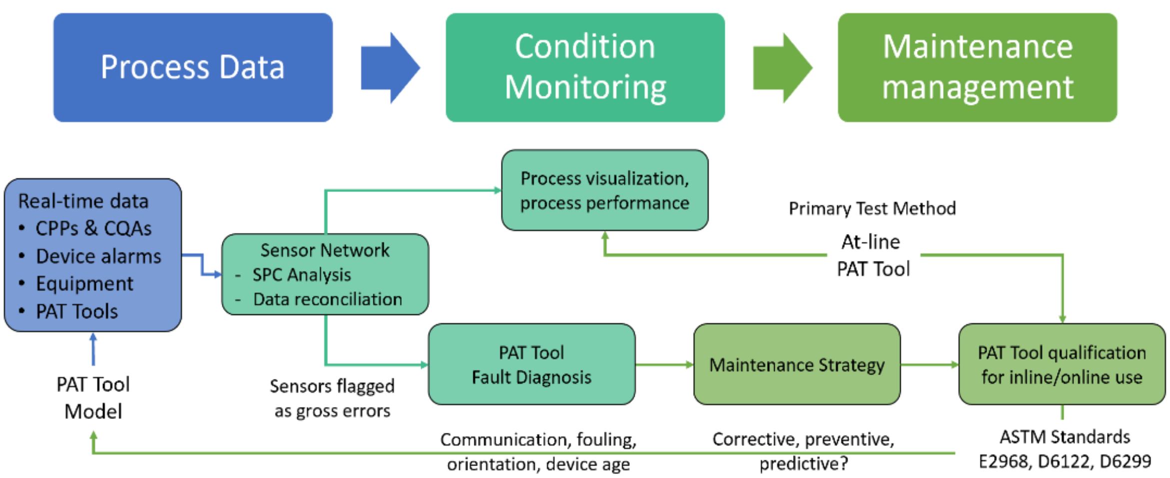

Figure 2: Integrated maintenance management for instrumentation systems in continuous pharmaceutical mfg.

occurrence of these faults, by analyzing the current and historical values of the process variables, local device alarms, visual inspections, and heuristics enable strategizing appropriate maintenance actions, and further configuring suitable improvements in the design and engineering of the systems used in the process.

Faults such as communication failures are detected using heartbeat tags configured at connection interfaces. A failure in communication is detected with unresponsive interface heartbeat and would require a corrective maintenance action. Further, it is important to note that instrumentation tools are a system of electronic components such as light source, optic cables, load cells, etc. Data such as spectra intensity, calibration history, load cell force variations and system knowledge provided by equipment and instrument vendors, and those gained during development and operations can be leveraged for configuring predictive maintenance of such components.

Importantly, conditions such as fouling and calibration errors, classified as gross errors, are detected by analyzing process data in real-time using data-driven and model-based methods (Venkatasubramanian, et al. 2003). Proof of concept in both simulation and experimental studies for continuous tableting process using sensor network analysis methods of data reconciliation and gross error detection were recently demonstrated for real-time process data validation, ensuring measurement accuracy, detecting sensor faults, and estimating unmeasured variables from our research group (Liu et al., 2018, Moreno et al., 2019, Su et al. 2019). This work utilizes these methods and leverages statistical process monitoring methods for configuring maintenance action to prevent a complete failure of the sensor system. The preventive maintenance strategies for in-process gross errors are optimized (Vassiliadis and Pistikopolous, 2001) to improve monitoring robustness further using the degree of redundancy and the average error of estimation as the key performance index for the sensor network (Bagajewicz, 2010) for reliable operations of the process. The above concepts are developed and implemented for continuous tablet manufacturing using the setup described for direct compression. Industry guidelines are followed to configure the reimplementation of the instrumentation tools.

Education & Additional Applications

The digitalization of the pilot plant also supports proof of concept and implementation applications such as material tracking, product risk analysis, lot release decisions, documentation, knowledge management, etc. for the development and application of process systems engineering methods to advance process design and operations in pharmaceutical systems. The pilot plant provides hands-on learning on automation systems for supporting the research activities in process monitoring, supervisory control, fault management, etc.

Further, the research learnings augment course modules as case studies and demonstrations in a graduate course on Smart Manufacturing. The established course on Computer Integrated Process Operations has been restructured to provide an overview of the process systems engineering methods, including advanced statistics and information technology in process operations.

Conclusions

The application and implementation of data-driven and model-based for sensor network fault monitoring, diagnostics and maintenance management for continuous tablet manufacturing to pursue fail-safe systems for process monitoring, supervisory control and product release decisions. The maintenance management of an integrated process consists of three actions in an integrated data-driven and model-based framework, as shown in Figure 2. First, process data is integrated and analyzed using methods such as data reconciliation, gross error detection, statistical process monitoring, etc. Second, gross errors are identified for their root causes for appropriate maintenance action. Third, to reconnect a maintained sensor, industry guidelines are configured to conform to industry regulations.

Further, the implementation of the framework using the relevant automation systems is demonstrated using pilot plant studies from the continuous direct compaction process at Purdue University. Finally, the research learnings leveraged to augment a graduate course focused on Smart Manufacturing is discussed.

Acknowledgment

The authors acknowledge the support of Ben Rentz and Dan Bao Le Vo for assistance in facility set up and operations; current group members Yasasvi Bommireddy, Prof. Marcial Gonzalez and Dr. Dhananjay Pai, and former group members for critical feedback; Rutgers C-SOPS, and our equipment, instrumentation, and automation partners for their continued support. We are grateful to the US-FDA for financial support through grant U01FD006487.

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