

Towards the Implementation of Condition-based Maintenance in Continuous Drug Product Manufacturing Systems

Abstract

Condition-based maintenance is a proactive maintenance strategy that prevents failures or diminished functionality in process systems through proper monitoring and management of process conditions. (Ganesh et al., 2020) Despite being considered a mature maintenance management strategy in various industries, condition-based maintenance remains underutilized in pharmaceutical manufacturing. This situation needs to change, especially as the pharmaceutical industry continues to shift from batch to continuous manufacturing, (Fisher et al., 2022) where the implementation of CBM as a maintenance strategy assumes a greater importance.

This dissertation focused on addressing the challenges of implementing CBM in a continuous drug product manufacturing system. These challenges stem from the unique aspects of pharmaceutical drug product manufacturing, which includes the peculiar behavior of particulate materials and the evolutionary nature of pharmaceutical process development. The proposed solutions to address these challenges revolve around an innovative framework for the practical development of condition monitoring systems. Overall, this framework enables the incorporation of limited process knowledge in creating condition monitoring systems, which has the desired effect of empowering data-driven machine learning models.

A key feature of this framework is a formalized method to represent the process condition, which is usually vaguely defined in literature. This representation allows the proper mapping of preexisting condition monitoring systems, and the segmentation of the entire process condition model into smaller modules that have more manageable condition monitoring problems. Because this representation methodology is based on probabilistic graphical modelling, (Bishop & Nasrabadi, 2006) the smaller modules can then be holistically integrated via their probabilistic relationships, allowing the robust operation of the resulting condition monitoring system and the process it monitors.

Breaking down the process condition model into smaller segments is crucial for introducing novel fault detection capabilities, which enhances model prediction transparency and ensures prediction

acceptance by a human operator. In this work, a methodology based on prediction probabilities was introduced for developing condition monitoring systems with novel fault detection capabilities. This approach relies on high-performing machine learning models capable of consistently classifying all the initially known conditions in the fault library with a high degree of certainty. Simplifying the condition monitoring problem through modularization facilitates this, as machine learning models tend to perform better on simpler systems. Performance indices were proposed to evaluate the novel fault detection capabilities of machine learning models, and a formal approach to managing novel faults was introduced.

Another benefit of modularization is the identification of condition monitoring blind spots. Applying it to the RC led to sensor development projects such as the virtual sensor for measuring granule flowability. This sensor concept was demonstrated successfully by using a data-driven model to predict granule flowability based on size and shape distribution measurements. With proper model selection and feature extraction guided by domain expertise, the resulting sensor achieved the best prediction performance reported in literature for granule flowability.

As a demonstration exercise in examining newly discovered faults, this work investigated a roll compaction phenomenon that is usually concealed from observation due to equipment design. This phenomenon results in the ribbon splitting along its thickness as it comes out of the rolls.(Mahmah et al., 2019) In this work, important aspects of ribbon splitting were elucidated, particularly its predictability based on RC parameters and the composition of the powder blend used to form the ribbon. These findings have positive ramifications for the condition monitoring of the RC, as correspondence with industrial practitioners suggests that a split ribbon is desirable in some cases, despite being generally regarded as undesirable in the limited literature available on the subject.

Finally, this framework was primarily developed for the pharmaceutical dry granulation line, which consists of particle-based systems with a moderate level of complexity. However, it was also demonstrated to be feasible for the Tennessee Eastman Process (TEP), a more complex liquid-gas process system with a greater number of process faults, variables, and unit operations. Applying the framework resulted in machine learning models that yielded one of the best fault detection performances reported in literature for the TEP,(Yin et al., 2012) while also introducing additional capabilities not yet normally reported in literature, such as fault diagnosis and novel fault detection.

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