

## ABSTRACT

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Title: Robust Process Monitoring for Continuous Pharmaceutical Manufacturing

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Robust process monitoring in real-time is a challenge for Continuous Pharmaceutical Manufacturing. Sensors and models have been developed to help to make process monitoring more robust, but they still need to be integrated in real-time to produce reliable estimates of the true state of the process. Dealing with random and gross errors in the process measurements in a systematic way is a potential solution. In this work, we present such a systematic framework, which for a given sensor network and measurement uncertainties will predict the most likely state of the process. As a result, real-time process decisions, whether for process control, exceptional events management or process optimization can be based on the most reliable estimate of the process state.

Data reconciliation (DR) and gross error detection (GED) have been developed to accomplish robust process monitoring. DR and GED mitigate the effects of random measurement errors and non-random sensor malfunctions. This methodology has been used for decades in other industries (i.e., Oil and Gas), but it has yet to be applied to the Pharmaceutical Industry. Steady-state data reconciliation (SSDR) is the simplest forms of DR but offers the benefits of short computational times. However, it requires the sensor network to be redundant (i.e., the number of measurements has to be greater than the degrees of freedom).

In this dissertation, the SSDR framework is defined and implemented it in two different continuous tableting lines: direct compression and dry granulation. The results for two pilot plant scales via continuous direct compression tableting line are reported in this work. The two pilot

plants had different equipment and sensor configurations. The results for the dry granulation continuous tableting line studies were also reported on a pilot-plant scale in an end-to-end operation. New measurements for the dry granulation continuous tableting line are also proposed in this work.

A comparison is made for the model-based DR approach (SSDR-M) and the purely data-driven approach (SSDR-D) based on the use of principal component constructions. If the process is linear or mildly nonlinear, SSDR-M and SSDR-D give comparable results for the variables estimation and GED. The reconciled measurement values generate using SSDR-M satisfy the model equations and can be used together with the model to estimate unmeasured variables. However, in the presence of nonlinearities, the SSDR-M and SSDR-D will differ. SSDR successfully estimates the real state of the process in the presence of gross errors, as long as steady-state is maintained and the redundancy requirement is met. Gross errors are also detected whether using SSDR-M or SSDR-D.