Abnormal Situation Detection in Batch Processes utilizing Projection Methods. Challenges for Pharmaceutical Applications

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Introduction

The FDA initiative on Process Analytical Technology (PAT) aims to improve product quality and process performance (manufacturing efficiency) in the pharmaceutical industry. FDA describes PAT as: *systems for the analysis and control of manufacturing processes based on timely measurements during processes of critical quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process.*

The approach described as PAT by FDA is an approach that has been taken by several other industries (petrochemical, polymer, chemical) several years ago. Timely measurements were collected during processes on process variables and other parameters. Process control techniques were developed. Attempts were made to understand the fundamental mechanisms of processes and built models. But it was not until 15 years ago, that the industry witnessed yet another revolution and managed to achieve (and exceed) the goals described by PAT. What made the difference was the ability to perform multivariate statistical process control (MSPC) and monitor the wellness of the process and product, by looking simultaneously at hundred of variables collected in real time.

Statistical process control looks at deviations beyond common cause variation. It operates on top of all the controllers. It will detect problems due to disturbances that could not be addressed by the controllers.

It is the experience of process industries that unforeseen disturbances play a major role in quality assurance. No matter how well one has understood the process, how sophisticated are the control schemes installed to ensure the required target quality of the product, how meticulous one is with the raw materials or the reproducibility of process, one has no control over some disturbances. What is the use of a very sophisticated control scheme (based on the measurements of an in-line analyzer) if the line has been plugged by impurities and the reading of the analyzer is wrong? How can we maintain the correct reaction temperature in the jacketed reactor if the thermocouple that feeds the readings to the controller fails? How can be sure in advance that everything will work as planned when it is common knowledge among practitioners that two reactors, designed identically will not perform the same?

Excellent results have been achieved, once the idea of multivariate statistical process control, that ensures process and product monitoring was accepted by industry. Over the last 15 years several industries managed, utilizing multivariate statistical methodology and analyzing all data collected

during production, not only to assure acceptable end product quality, but also to improve process performance and maintenance.

Why combine process and quality information ? Statistical Process Control vs Statistical Quality Control.

Consider the jacketed reactor shown in Figure 1. The flow rate (F) of the cooling / heating agent is regulated by the value of the reactor temperature measured by thermocouple T_1. There are 3 thermocouples in the reactor in three different locations. We also measure pH and degree of agitation (RPM).

Traditionally the performance of the process is assessed by monitoring certain product quality properties off–line and sometimes only at the end of the run. By monitoring only the quality variables one performs statistical quality control (SQC). Quality properties of the product as well as the progress of the process can also be monitored in real time by utilizing in-, at- and on-line analytical instrumentation. Examples are UV-VIS and NIR spectroscopy and ultrasound. By introducing more frequent quality data using real time analyzers, one still performs SQC. Once it is detected that the product properties are no longer consistent with the specifications, it is not easy to identify the process variables responsible for the deviation. Real time analyzers provide *product quality* information; but what about *process quality* ? What if the analyzers fail? How do we know that the readings we get are reliable?

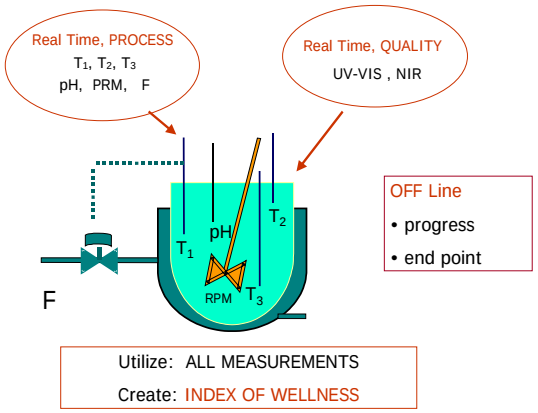

Figure 1

For true statistical process control (SPC), one must look at all the process data as well. Measurements on other variables such as temperature, pressure, pH as well as measurements on the mechanical and electrical parts of the process (agitator power, pump speeds, etc.) often exist that can also contain very important information; these measurements also reflect the state of the process. These frequent process measurements are usually ignored. Monitoring the process variables is expected to supply much more information on the state of the process and to supply it more frequently. Furthermore, any abnormal events that occur will also have their fingerprints in the process data. Thus, once an abnormal situation is detected, it is easier to diagnose the source of the problem, as we are dealing directly with the process variables. Information about the process may also include the vessels used for a specific run, the operators that were on shift, suppliers of raw material, etc.

To illustrate the need of monitoring process measurements an example scenario for the reactor of Figure 1 will be used. Suppose that the thermocouple T1 fails; it keeps showing the same temperature which is higher than the true one in the vessel (although its value is within the expected range for this thermocouple). As a result the valve opens to allow more and more cold water to come in. It will take sometime before the effect is reflected on the product quality; and after the deviation in product quality is detected, it will take sometime before the operators determine the cause of the problem. However, if we were monitoring all the three temperatures, the flow of cooling agent, etc, then the fact that the other two temperatures were showing a different value than T_1 would have raised an alarm. Also agitation values would have shown that the degree of agitation does not justify such differences of temperatures between thermocouples and therefore something else is going on.

For the case of the pharmaceutical processes, on-line measurements on temperatures, pressure, pH, RPM, etc., combined with on-line measurements from analytical technology (spectroscopy, ultrasound, etc) will lead to on-line process monitoring and make multivariate statistical process control, fault detection and isolation, possible. Combining information from the process measurements with the information from the analytical tools gives a very powerful tool to monitor the process. These two sets of measurements are not independent from one another, but interrelated. As a matter of fact these measurements "confirm" each other. For example, one may use an analyzer to monitor conversion during the process. If other process measurements are also monitored, say the temperature and the pH, we built a picture of the relation between conversion, temperature and the pH values, for the duration of a typical run. If at some point this relation breaks, we may assess that something "unusual" is happening at the process.

Another advantage of monitoring process data is that in some cases, the few properties measured on a product are insufficient to define entirely the product quality. Take an example from the polymer industry: if only the viscosity of a polymer is measured and kept within specifications, any variation in end-use application that arise due to variation in chemical structure (branching, composition, end-group concentration) will not be captured. In these cases, the process data may contain more information about events with special causes that may affect the product structure and thus its performance in different applications.

Finally, by monitoring process variables other abnormal operating conditions may be detected, as for example a pending equipment failure. In other words one could monitor the wellness of the process itself. The example presented earlier with the failure of the thermocouple in Figure 1, is a case for a failure that would have been detected and corrected (by switching and feeding the controller the other thermocouple measurements) before the product quality would have been affected.

Monitoring hardware failure is not the only reason to monitor the process. Sometimes process variables may *replace* an analyzer. This is the idea of *soft sensors*. In many monitoring and control situations we are often lacking real time sensors capable of measuring many of the responses of interest, because the measurement equipment for such quality variables may be very expensive, or difficult to put on-line, or costly to maintain. As a result we often try to develop *soft sensors* or inferential models which use other readily available on-line measurements such as temperatures, and can be used to infer the properties of interest in a real time manner. These soft sensors can either replace the hardware sensor (analyser) or be used in parallel with it to provide redundancy and verify whether the hardware sensor is drifting or has failed. When used in parallel the soft sensor will either estimate the property and compare its value with that of the analyser, or it will keep track of the correlation between the analyser reading and the process measurements. An example where a soft sensor is used to assess the reliability of an analyser is presented later.

Using the soft sensor philosophy, one could go a step further, and instead of measuring a specific property, one could create a soft sensor to "keep an eye on the process". That is, to monitor "the wellness of process & product quality" and to do that by using all the available measurements.

This can be achieve utilizing projection methods (latent variable methods) which exploit the main characteristic of process databases, namely that although they consist of measurements on a large number of variables (hundreds), these variables are highly correlated and the effective dimension of the space in which they move is very small. In the example of Figure 1, although we have 3 measurements of temperature (3 thermocouples), all the measurements are correlated and reflect upon one event – the temperature fluctuation due to the exothermic reaction. Typically only a few process disturbances or independent process changes routinely occur, and the hundreds of measurements on the process variables are only different reflections of these few underlying events.

Multivariate Statistical Process Control in Industry.

Traditionally statistical process control in industry, has been synonymous with monitoring product quality variables or some key process variables in a univariate way. The direct result of this is the large number of control charts that are usually present in a control room and that the operators have to attend to. When there is an abnormality in the plant operation several of these charts alarm in a short period form each other, or simultaneously. This happens simply because process variables are correlated, and an abnormal event may affect more than one variable at the same time. When such a situation occurs, it is difficult for the operator to isolate and determine the source of the problem, which may lie with only one of the many correlated alarming variables, or, as it is most frequently the case, it may simply be a non measurable variable (impurities, plugged pipe, blockage of a sensor) that causes several other measured variables to go out of control.

The use of projection methods for the last 15 years has revolutionalised the idea of statistical process control for multivariate processes. The performance of an entire unit, or even a plant, can be monitored by the operator looking at only a few multivariate control charts, that can be thought of as process performance indices. These charts, which are based on latent variables are simple, easy to understand by the operators and have found quick acceptance in the control rooms. They improve early fault detection capabilities, because they are able to detect the onset of a fault at the same time as, but in most situations earlier than, the many univariate charts. More importantly however, they detect problems that manifest themselves as changes in the covariance structure of the process variables, which univariate charts will miss if the variables remain within their expected univariate operation limits. The methodology based on latent variables also provides diagnostic tools that help the operators determine quickly and efficiently the source of the problem.

The last 15 years have seen an upsurge in interest in the application of multivariate projection methods to analyze databases accumulated in industry in order to improve process performance and product quality, as can be seen from the number of industrial publications and patents (references can be found in Kourti, 2004a). Improving the operations of existing processes involves developing better methods for the analysis of historical operating policies, process troubleshooting, process monitoring, abnormal situation detection, fault isolation, and process and product optimization.

Data collected from processes are highly correlated (many variables being collinear) and non-causal in nature; the information contained in any one variable is often very small due to low signal-to-noise ratios; and measurements are often missing on many variables. Multivariate projection methods address the above problems in a straightforward manner and provide analysis tools that are easy to present and interpret. Latent variable methods that exploit the correlation of process variables, and therefore model the structure of the process space, are extremely powerful when dealing with two

other problematic characteristics of industrial historical databases, namely missing data and low content of information in any one variable (due to the low signal-to-noise ratios).

The methods and their potential and limitations for improving operations for both batch and continuous processes, are discussed in Kourti (2002, 2003a, 2003b, 2004a, 2004b). Examples from state of the art major industrial applications currently running online are presented to illustrate the tremendous potential of these methods. The above articles also contains an extensive literature review on the subject and also include practical considerations for the user as well as warnings for potential pitfalls, from data acquisition to modeling to on-line application. The industrial practitioners perspective can be found in Nomikos (1996), Miletic et al. (2004).

Multivariate Statistical Process Control in Batch Processes

Multivariate charts have superior detection capabilities to univariate charts for batch processes. In the words of a colleague from industry: "In most cases in practice, changes in the covariance structure precede detectable deviations from nominal trajectories. This was the problem that univariate monitoring approaches for batch processes could not address. In most process upsets it is the correlation among the monitored variables that changes first, and later, when the problem becomes more pronounced, the monitored variables deviate significantly from their nominal trajectories. There are cases where a process upset will change dramatically only the correlation among the variables without causing any of the variables involved to deviate significantly from its nominal trajectory. These particular cases, although rare, can result to significant cost to a company since they can go unnoticed for long periods of time (usually they are detected from a customer complaint)". (P. Nomikos, personal communication, 2002).

Industrial applications for batch analysis, monitoring and fault diagnosis have been reported. (references in Kourt, 2003b and 2004a). It should be noted here that several companies choose to use the methodology not for on-line monitoring but as a tool for *real time release* of the batch product. That means that the batch is not monitored as it evolves; rather, immediately after the batch finishes the process data are passed through the model and the scores for the complete batch are investigated. If they are within control limits the product is released. If there is a problem, the product is sent for analysis in the laboratory. This procedure saves the company time and money. The batch run may last 2 hours but the product analysis may take 8 hours. That means that they do not have to waste 4 batches while they are waiting for the results from the laboratory. By checking the process data as soon as the batch is complete, they can detect problems before starting a new batch.

Challenges

There are several practical considerations to be addressed when embarking in a task like the PAT initiative. Some of the problems are already solved in other industries and the solutions can be adapted for the pharmaceutical industry. Other problems will require further research. These challenges will be discussed in the conference.

Summary

Multivariate Statistical Process Control can become a powerful tool in the Pharmaceutical industry. Real time and off-line measurements from analytical technology when combined with process data in a meaningful way, can provide a robust tool for real time monitoring of process and product performance. Lessons can be learned from other industries where such combinations led to

multimillion dollars of savings. Older methodologies can be adapted to meet the needs of the Pharmaceutical Industry, whereas new research will be required to meet new challenges.

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