Can Assumption-Free Batch Modeling Eliminate Processing Uncertainties?

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Today, univariate control charts are used to monitor product characteristics and key process variables throughout processing. Unfortunately, these variables are, in most cases, not independent of one another and do not necessarily characterize product quality accurately. The ideal solution is to apply a method that not only uses multivariate data analysis (MVA) but also uses the batch trajectory to predict development in real time rather than relying on assumptions.

Monitoring batch processes to ensure the highest level of quality is imperative. While periodic batch process control is the traditional approach to managing consistency end quality, it is recipe-driven. The operations are, in most cases, not automatically adjusted to accommodate raw material variations, changes to uncontrollable factors, and other circumstances. This creates significant challenges for maintaining consistency and quality from batch to batch.

Today, univariate control charts are used to monitor product characteristics and key process variables throughout processing. Unfortunately, these variables are, in most cases, not independent of one another and do not necessarily characterize product quality accurately. For example, in process development, experimental plans are used to estimate the effect of different design variables and their interactions using statistical methods. This data can be analyzed and the effects of the variables can be estimated. However, the challenge is knowing what happens to the process if uncontrolled sources of variation are present, such as changes in chemistry or biology, a mechanical failure, or simply a misstep by an operator. The ideal solution is to apply a method that not only uses multivariate data analysis (MVA) but also uses the batch trajectory to predict development in real time.

Applying this type of approach allows visualization of how the process evolves independently of the sampling rate and enables plotting of individual variables

in relative time. It also eliminates any assumptions about the synchronization and duration of batches. This solution increases product development efficiency and answers the call of the FDA to better understand and control the manufacturing process through the application of process analytical technology (PAT).

Below are four significant issues with current batch modeling approaches that can affect product quality and efficacy:

❶ Most batch modeling approaches assume equal lengths of time for each batch with the same number of time points for each batch.

For monitoring a new fermentation, you will likely have no idea how long the process will take. The length of time it takes to process is also not enough information to assume the batch's state in terms of chemistry or biology. Numerous approaches to handle uneven batch lengths exist, such as replacing time with a maturity index, dynamic time warping, and time linear expanding/compressing. Complications can occur in all of these methods if the new batch does not start at the same chemical/biological state.

Using an assumption-free modeling approach, batch progression is monitored in real time. The status of all variables is monitored to ensure their behavior at any given point of time is as expected. If there is an unexpected change in any of the variables, the system allows the operator to determine the cause and take action using a control feedback loop system.

AN ANALOGY — BOILING WATER

Assume a scenario where water must be heated to boiling (212° Fahrenheit) across different parts of the world. Depending on the region, the starting temperature of water could be very frigid, such as 35° in Norway, or very warm, such as 87° during a Florida summer. Each starting point is different, just as it is in chemical reactions or fermentation processes. Therefore, one cannot simply plot each temperature curve starting with the sample number. What can be done instead is to model all curves when they have reached the common starting point (87°) and up to the boiling point.

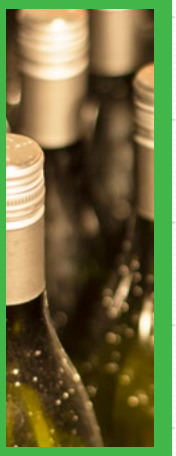
❷ Multiphase stages exhibit non-linear system dynamics, which makes modeling of phase transitions challenging.

Today's methods assume linear relationships in batch processes, which is fundamentally incorrect as the progress of a chemical reaction or fermentation process may not develop linearly over time. When these types of processes are modeled with traditional modular methods, a linear relationship is being forced. Because cells may double in numbers during the growth phase but eventually stop, this creates challenges in monitoring the process in terms of the sample number/time.

With multivariate batch modeling, linearity with regard to time is not assumed. Instead, the non-linear parts of a batch may be handled directly or can be monitored individually, thereby eliminating the false positives and errors seen with a traditional method.

AN ANALOGY — FERMENTATION

Fermentation is an example of a process that happens in multiple phases where linearity is often forced. In the initial phase, the starter culture is fed until the optimal environment is created. This is when the growth phase begins, and the number of cells increases exponentially. Once maximum growth has been reached, the stationary phase begins and the cells remain at that number. Each of these phases has a different profile, and they are not directly related to time. When monitoring a fermentation process using today's traditional modular method, a straight line is being forced through that data, resulting in inaccurate information and a potentially damaging impact on the product.



❸ Frequency of observations is not always consistent from batch to batch.

Today's methods focus on analyzing data based on a certain number of observations. Any alignment or re-sampling of the data will distort the chemical or biological information captured to some extent. An example of this is a case where the sampling rate is varied between the batches and thus the sample number does not reflect the batches' development over time, even if the relative states were the same. The situation where the sample number does not reflect the same state is more a rule than an exception for chemical and biological systems.

With assumption-free batch modeling, the batch is not monitored in absolute time but in the relative time required for the batch to achieve the required chemical or biological state. When the model has been established, it can be used in real time to determine if there are any variations from the behavior a normal batch would follow. This normal batch is based on the observation of a pattern of multiple different variables. If no variations are detected, the manufacturer can have confidence that the end product has the defined quality that is expected. Any deviations from the desired behavior are recognized immediately.

❹ The true end of a reaction cannot be identified, thereby increasing production time and operator responsibility.

Determining when the end of a reaction is reached can be very challenging, especially in the pharmaceutical industry. For example, to produce a tablet, a combination of liquid powder molecules and other various chemicals are mixed to form granules, which must then be dried. The drying process requires exposing the granules to hot air until a specific level of humidity is reached. In this scenario, a specific drying time for the granules is set. If the humidity level during that time decreases below the required level, the result can be a significant failure at a later stage when the tablet is compressed. Because of this, operators are required to conduct frequent checks to ensure the appropriate humidity level is maintained. Not only does this add time to the process, but it also leaves a considerable amount of uncertainty when it comes to exposure times.

With an MVA approach, a modeling strategy utilizing probes that continually monitor the humidity level during the drying process can be applied. When the true end of the drying process has been reached, the operator is notified and the process is stopped, increasing both efficiency and accuracy. Most importantly, the more you dry, the more this affects yield as materials can eventually become too brittle.

Batch processes are common in many industries, and, especially in the pharmaceutical industry, it is imperative the data retrieved from these processes is accurate. Camo Software's batch modeling approach (a new add-on to their MVA and process monitoring software suite, Unscrambler®) provides users with a better and more accurate tool when working with batch

data, especially when monitoring new batches in real time to detect out-of-spec situations. Adapting batch operations according to any detectable changes during processing provides a control mechanism to drive a product towards its desired state, thereby achieving the best possible end product quality.

SUMMARY OF KEY BENEFITS

❶ EVENT DETECTION — An MVA modeling approach offers an ability to monitor the progress of a production process to proactively identify deviations or faults that would lead to bad product quality. This allows the problem to be fixed before the product is ruined.

❷ PROCESS UNDERSTANDING — Through this approach, you can appropriately model a process to capture the overall state of your products and to, therefore, better understand the processing conditions you need to use for future production and the optimal settings. The approach also provides a more realistic view of a process than the more commonly-used approaches, where the different plots are projected on the same timeline and do not reflect the relative time.

❸ PROCESS DEVELOPMENT — The desired state of the end product is the ultimate goal of a process. Therefore, the process must be stopped at the correct time to achieve the correct level of quality or composition of materials. In many cases, processes continue longer than necessary (after the process has reached its final state), which takes up unnecessary capacity in a production environment, ultimately prolonging the production.

❹ QUALITY CONTROL — When a process is designed to meet the level of quality required by regulators, it is often assumed that every batch created with that process will fit those quality standards. Unfortunately, this is not always the case. By using MVA, all of the effort put in during development to design quality into a product is not only maintained but also improved during production.

ABOUT

CAMO Software, makers of The Unscrambler® X software, delivers multivariate analysis software and solutions for analyzing large and complex data sets quickly, easily and accurately. World-leading organizations rely on our solutions to get deeper insights, understand processes and make better predictions from their data. Established in 1984, we are pioneers and leaders in the field of multivariate data analysis.

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