Biomanufacturing Complexity

A complete systems approach is the key to understanding and then dealing with complexity

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Introduction

Biopharmaceutical manufacturing is characterized by significant, and at times overwhelming, complexity, from the intricacies of the technology itself to the need to understand many interacting processes and systems. Biotech facilities also have unique challenges not seen in any other industry. It is a constant struggle to remain flexible under the constrictions of GxP validation and heavy industry regulation.

In this complex environment, seemingly minor changes can have massive impacts on facility utilization, utilities consumption, variability and risk of contamination. In this whitepaper, we discuss ways of modeling the complete system and, as a result, managing complexity in biomanufacturing facilities. Modeling can be used by your organization to find bottlenecks, increase throughput, lower risk, and accurately understand outcomes that can be expected from process changes.

Inherent Biological Variability

Biopharmaceutical manufacturing is a fundamentally different paradigm from other high technology manufacturing industries. While other industries also have to cope with yield and manufacturing variability, much of this variability can be engineered or designed out of the process. Biopharmaceutical manufacturing, on the other hand, uses living organisms to grow target molecules. Those living organisms are imperfectly understood, as are the exact conditions they require for optimal growth. This means that variability is inherent to the biomanufacturing process. That variability needs to be completely envisaged if bottlenecks are to be found and throughput and other metrics are to be improved.

Inherent biological variability has a number of effects on a biopharmaceutical manufacturing facility. First, it means that processes must be designed to monitor and manage this variability. A large number of parameters must be tracked in order to understand the production process, and this massive amount of data is often difficult to understand. Automation systems, designed for ‘widget’ manufacturing, are often ill-suited to this production and must be custom-finished or designed.

Second, variability requires the separation of upstream (fermentation) and downstream (purification) processes, with column cycling and other downstream steps contingent on the quantity of material produced. This means that variability in one section of the plant is seen in many other areas, creating a ‘magnifying effect’ where small changes may lead to large delays or disruptions to processing.

Third, biological processes carry with them relatively high risks of contamination and batch loss when compared with other industries (such as the semiconductor industry). Biomanufacturing has a long record of contamination events causing single batch losses or even entire facility shutdowns. Genzyme’s 2010 viral contamination, and associated $175MM fines, is just one example of biological variability causing complications to biopharmaceutical manufacturing.

Inherent biological variability creates significant complications in the number of parameters that must be tracked both in automation systems that control the process and in performing any kind of ‘what-if’ analysis on the facility. In the next section, we discuss the effect of variability and complexity on biopharmaceutical operations.

Effect of Variability and Complexity

Biopharmaceutical manufacturing carries with it significant variability and complexity, but what is the effect of this complexity on operations? The answer in many cases, is ‘none.’ The answer in some cases, is ‘significant.’ One of the classic issues in biomanufacturing is that apparently small changes to a unit operation can have large changes to overall throughput or some other key performance indicator.

Case study: WFI modeling

Take as an example a case study involving WFI consumption at a large biopharmaceutical manufacturer. The manufacturer had been running a product in their facility for quite some time, but wanted to increase the run rate of the product from 2 batches per week to 2.2 batches per week – a relatively modest 10% increase. The manufacturer wanted to confirm that WFI generation capacity would be sufficient to meet the 10% increase in throughput.

Emerson performed a simulation analysis incorporating the variability at the facility. The data showed that a 10% increase in throughput was possible at the facility, but would require the plant to operate much more closely to its designed capacity. This meant that significantly less 'white space' was available to absorb delays in unit operations, and without this extra time, delays quickly accumulated. The result was a significantly less predictable schedule and more opportunistic cleaning, steaming and other supporting activities.

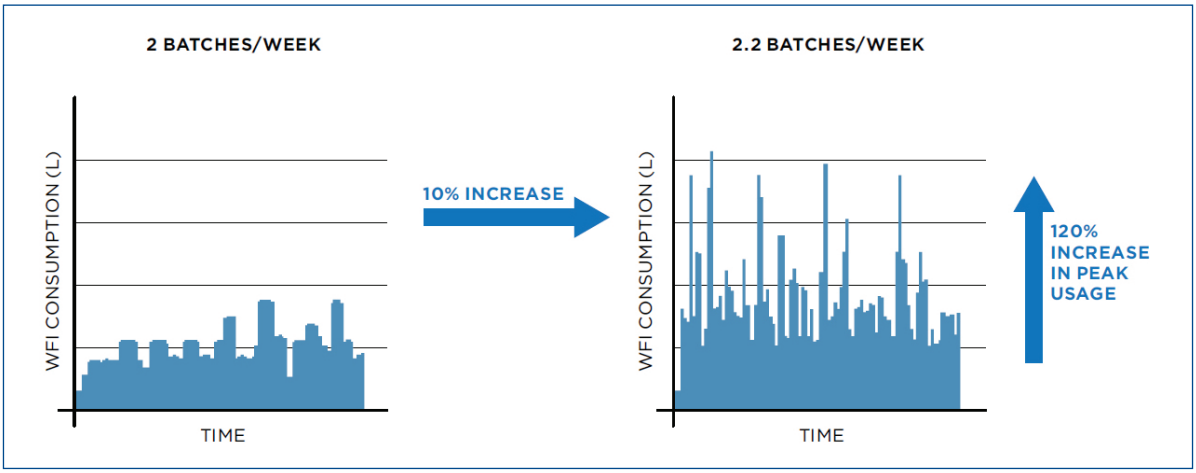

Figure 1: WFI Modeling Analysis, 10% increase in throughput means, 120% increase in peak WFI usage

Figure 1 above shows the outcome of the analysis, indicating that a 10% increase in throughput required a 120% increase in peak WFI consumption – exceeding the facility's WFI generation capacity and requiring extensive modifications to the facility. Emerson's Director of MES, David Zhang, David Zhang comments: "people forget that apparently small changes to a biomanufacturing facility can have massive impacts. In this case, a 10% plant speedup translated to significantly less predictable performance, resulting in massive need for instantaneous generation capacity."

Case studies such as these are replayed across the biomanufacturing industry, with many firms modeling some areas of the facility in excessive detail while leaving out critical areas that are beyond the scope of most toolsets. Utilities, supporting activities such as media and buffer preparation, glass washing and autoclaving, and transfer panels are examples of areas of the facility that receive too little attention. A complete systems approach is needed so all variability is envisaged.

To Fix a Problem, You Must First See the Problem

Emerson's focus has first and foremost been to understand complexity through automated analysis of raw data. There are a large number of data

sources in the modern biotech enterprise – automation, MRP and ERP tools, as well as measurement systems – but it is often difficult to understand and make sense of how these data streams should be used to make better decisions.

Worse, despite the huge array of data 'available,' very little of the data is actually accessible in a usable format, or is searchable across the enterprise. This particularly applies to a critical element of complexity: processing times in the facility. "When we first started asking for timing data, no one had it," comments Principal Rick Johnston. "pH and temperature were easy to find, but to find out how long a buffer preparation took was almost impossible to find."

Case study: SIP durations

Figure 2 shows the steam-in-place (SIP) duration of a tank, including a jump in processing times in 2007 by nearly 1 hour on average (this data is indicative only). While this graph clearly shows the jump in process times, making this data visible to the business required several hours of analyst time: first to extract the data from DeltaV, then to exclude a hold step which was not part of the process, remove outliers caused by SIP skid restart, and finally group the data for presentation.

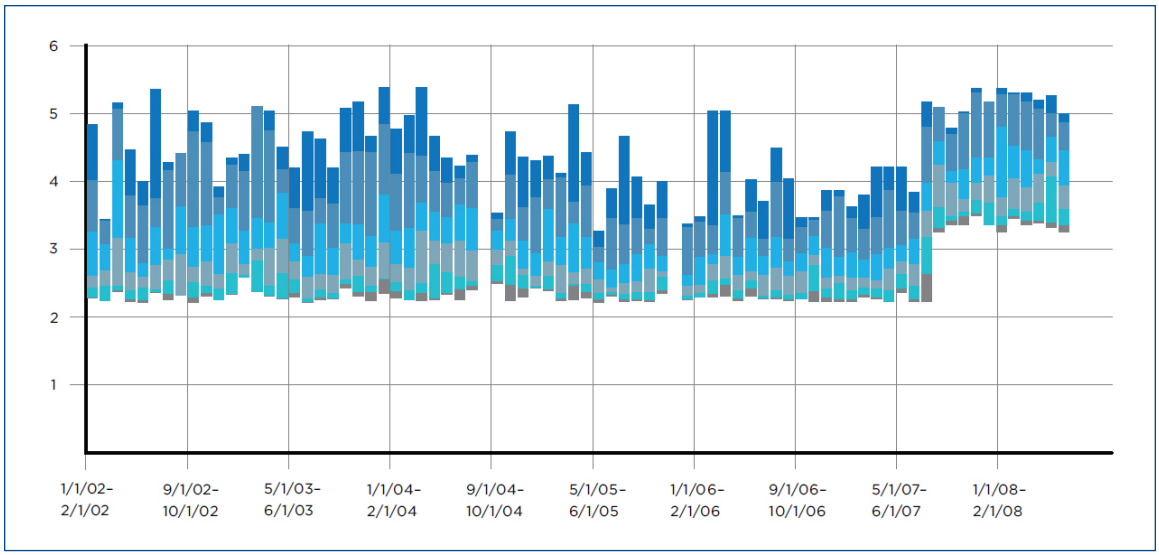

Figure 2: Steam-in-place durations for a tank, monthly percentiles of sip, durations, 2002 to 2008

Figure 2 uses a key metric for SIP – the duration of the activity – as a proxy for how that activity is performing. A longer time means delays in other SIPs, as well as returning that tank to a 'ready' state for further cleaning. In this case, seeing the data showing increased process times allowed the biotech manufacturer to make investment in disposables technologies to decrease dependency on the SIP skid.

Managing Operations Through Modeling

The WFI and SIP case studies above show examples of when comparatively small process changes can have significant impacts on key performance metrics. This 'non-linear systems response' means that it is very difficult to predict the impact of a change to the facility. As a result, leading biopharmaceutical companies are increasingly implementing modeling toolsets to understand their operations.

These modeling frameworks are designed to take data from a variety of sources, perform aggregation, and translate that data into a usable model that can assist the business. Examples include SAP's APO (advanced planning and optimization) toolset – a finite scheduler for supply chain, Intelligen's Superpro designer – for chemical and mass-balancing of manufacturing facilities, as well as Excel-based toolsets like Biopharm Services 'BioSolve' suite. One of the main challenges of such toolsets is that they are typically used in ways they are not originally designed for, and to answer questions that may not be the critical areas of need for the business.

Systems-based Modeling Approach

Optimizing the biomanufacturing process requires a shift in thinking to a systems- based approach where the entire manufacturing operation can be seen and analyzed inside a single toolset. This allows organizations to prioritize focus around the key areas of the manufacturing process that are critical to process optimization, rather than pursue projects that deliver localized value to only one area. We discuss the key aspects of a successfully implemented "complete systems" approach below.

Use only real data to make decisions

Rather than use theoretical data and average process times, modeling systems need to directly integrate with manufacturing data. That means engineers discuss what is actually occurring in the facility, rather than their perception of a manufacturing operation. This data-driven approach is already well- embedded in drug development and discovery, but needs to be relentlessly pursued in operations to ensure the critical aspects of the process are correctly modeled. Using real data also requires models to incorporate variability into their design, so the effect of process variations can be clearly understood.

Model everything, but focus on the variables with the most impact.

Managing complexity requires users to quickly find the variables that affect key metrics. In the graph below, an analysis of a model involving over 200 activities revealed that only 10 of those activities had a significant impact on throughput. Pursuing a systems approach to modeling requires accurately representing all of those 200 activities, but focusing engineering resources only on those 10 activities that actually deliver value to the facility.

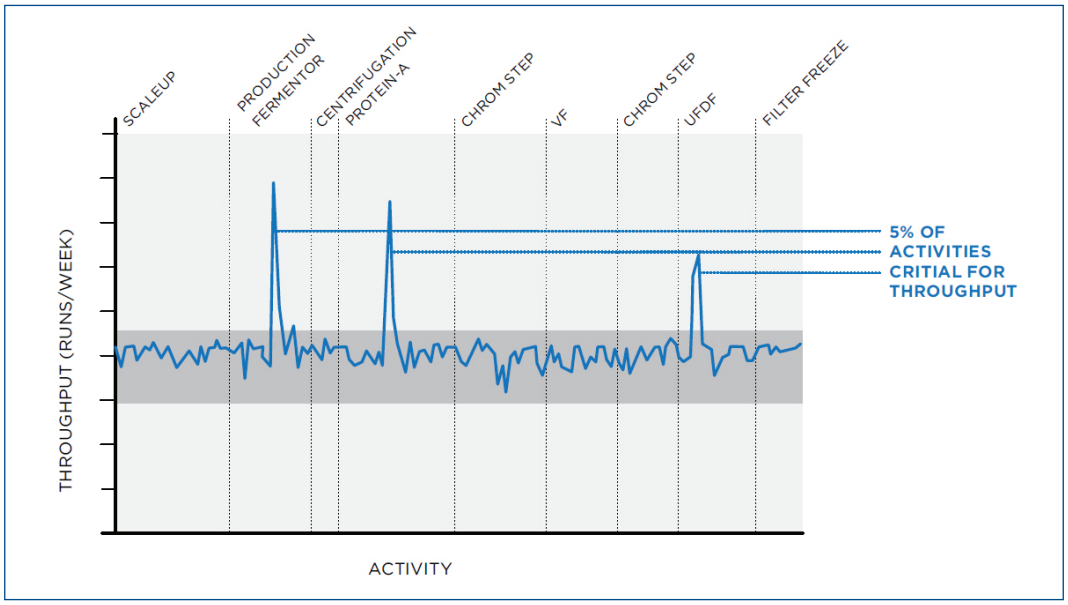

Figure 3: Identify ing the critical activities in a facility that affect throughput spike chart of critical activities in the facility that affect throughput

Cross-functional modeling

One of the patterns that Emerson has observed across biotech manufacturers is a tendency for different operating groups to solve their own perceived issues. Such a 'silo'-based approach ignores the fact that all these groups are working on a common problem: to deliver the right quantity of material safely and on time to their customers. This requires model development to be cross-functional, involving manufacturing sciences, operational excellence, and supply chain groups. Without such an approach, models are built to solve local problems and can actually be detrimental to the overall goals of the business.

Case Study: Implementing a 4 G/L process

The challenge many biomanufacturers are currently facing is that their existing manufacturing capacity assumes a fixed titer. While many can express titers of 2 grams per liter and above, the ability of existing purification equipment to process that quantity of protein in one run is strictly limited. The key challenge for one large biotech manufacturer was to retrofit their current production plant to allow much higher titers to be processed. Emerson's brief was to evaluate the different retrofit options and determine the optimal strategy to maximize return on investment.

Emerson's model included variability seen in the facility and compared against an deterministic model without variability. The results were compelling, first showing that without variability, the model incorrectly picked the best result (and also overestimated the true throughput). Conversely, Emerson's analysis suggested the best solution, yielding results within 5% of the implemented approach. Based on this recommendation, the facility increased overall throughput by 10-15% with a return on investment of $60MM over 4 years.

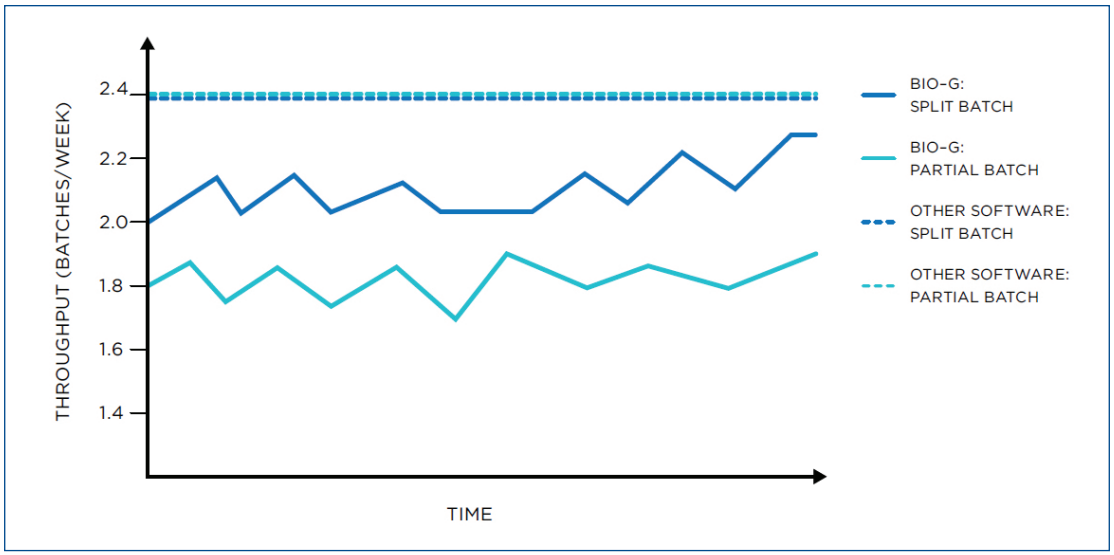

Figure 4: Comparing Split batch vs. Partial batch processing analysis with variability shows the effect of Split batch vs. Partial batch processing

Conclusions

Biopharmaceutical manufacturing is a complex industry requiring the aggregate skills of many different disciplines, operating in a tightly regulated and highly controlled environment. In such an environment, complexity is a way of life. The biological nature of the process, the comparatively small number of batches produced, and the risks of contamination all create additional complexity that must be understood.

In such an environment, modeling toolsets are of critical value. These toolsets are our ‘eyes and ears’ to the facility, enabling us to integrate real-world data with models to understand and probe the impact of changes. Emerson's software approach aims to directly address the needs of the biopharmaceutical manufacturing sector, with toolsets that collect and display data, provide best-in-class analysis of biomanufacturing facilities, and allow the analyst to quickly see and understand how that complexity will affect changes. Such an approach results in finding hidden bottlenecks, increasing throughput, and mitigating risk with a high degree of accuracy.

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