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Process Simulation and Modeling Strategies for the Biotechnology Industry

Optimizing Productivity in Multiproduct Batch Facilities

Ian Gosling, Ph.D.
www.chemsim.com

Process simulation and modeling is the application of a range of software tools to analyze individual unit operations (or process stages) and their relationships within the overall process. This relationship includes assessing the resource and utility requirements available from the host facility. Once simulations (or models) are constructed, process engineers and scientists can investigate complex and integrated biochemical processes and unit operations, without the need for extensive experimentation or disruption to existing operations. These tools can be used at all stages of process development, from conceptual design, through process operation and optimization.

In the tightly regulated field of biopharmaceuticals the primary concern is production throughput and optimum use of limited facilities. Demanding questions arise from the increasing use of flexible multi-product facilities and contract manufacturing. Methods are required to effectively and economically allocate resources and utilities for competing parallel processes. Applying process simulation to maximize the utilization of resource-constrained multi-product facilities can therefore yield profound economic benefits for biotechnology companies.

Modeling Tools

Today the largest supplier of simulation software to the biotech and pharmaceutical industry is Microsoft (Redmond, WA), which offers several basic software tools that can be used for simulation:

1. Visio® - Constructs flow sheets with a drawing package
2. Excel® - Process calculations are performed with spreadsheets and reported graphically
3. Project® - Constructs process schedules and labor assignments

The disadvantage of these tools is that they are not designed for bioprocess simulation. Icons for the various operations are not readily available and simulations using Excel® often result in rather large and often unwieldy spreadsheets, which are difficult to maintain and document. The popularity of these tools is due to their low cost and familiarity to users. Using these tools for simulation of multi-product resource constrained facilities can become extremely time-consuming. There are several process simulation software packages available commercially. Of these, only a few are directly applicable to bioprocessing. Still fewer combine simulation with the capability to provide scheduling of competing parallel processes within the same facility.

Aspen Technology (www.aspentech.com) originally created a dedicated Bioprocess Simulator (BPS), which was eventually phased out and replaced by Batch Plus, a recipe-driven modeling environment for batch processes. Batch Plus can perform complex simulations on multiple batches in a manufacturing plant to determine the total demand on shared resources. Batch Plus is just one product in a suite of engineering software products offered by Aspen Technology.

Hyprotech (Calgary, Canada) offered BaSYS which consisted of software and services to manage batch information. Since Aspen Technology acquired Hyprotech, BaSYS will be incorporated into Batch Plus and, according to company press releases, the two will be combined to produce Aspen Batch+.

SuperProDesigner from Intelligen (Scott's Plain, NJ) combines the drawing, calculation and scheduling features of the three Microsoft packages listed above into a single, moderately priced package. SuperProDesigner also offers a database feature to log equipment and utility capacities. This package has the added advantage that it was specifically developed for simulation of biopharmaceutical process unit operations and processes. It is user friendly and set up to capture the unique unit operational data requirements of biological processes.

The dedicated process simulation packages described above have made strides to increase their ability to interface with common software tools. Results from these packages are now exportable to spreadsheet format, schedules are exportable to Project®, and flowsheet drawings are exportable to a range of formats, and are compatible with many of the CAD drawing packages.

Statistical Treatments

Statistical approaches to process simulation are gaining popularity as biotech and pharmaceutical companies search for ways of characterizing processes with many variables. For processes where the mechanistic models are not sufficiently developed a statistical treatment is a valid alternative approach.

An advanced statistical technique is to construct a neural network model of the process. Gensym (Burlington, MA) offer a customizable neural network framework NeuronLine, which is built upon their well-tested G2 platform.

For applying Monte Carlo based statistical simulation, the tool of choice is Crystal Ball® from Decisoneering (Denver, CO). As a fully integrated Excel add-in program with its own toolbar and menus, Crystal Ball performs Monte Carlo analysis on data in a spreadsheet format.

Design-of-Experiments (DOE) is another technique used to statistically characterize the process to produce a mathematical representation. Adjusting input values and measuring the results can test productivity improvements, or the system can be used to predict the

effects of operating parameter excursions. An example of DOE software is Cornerstone™, from Brooks Automation (Chelmsford, MA), a supplier of manufacturing software used in many industries.

Scheduling

As more biopharmaceutical products are moving out of the lab and into production, contract manufacturers are scrambling to expand their operations. If the manufacturers can optimize the use of their current facilities, they can increase throughput and thus increase profits, possibly deferring the expensive costs and delays of expansion.

To optimize productivity in a multi-product, contract-manufacturing facility where processes are run in parallel requires a large degree of overlap between batches, and effective utilization of shared resources and equipment. In fact the complex batch, multi-process, constrained optimization problem is becoming one of the most important problems in design and optimization of production facilities in biotechnology.

For example, in biologics manufacturing purified water is used in significant quantity and is often a limiting resource – especially when multiple parallel cleaning operations are required. Clean-in-place (CIP) systems usually clean one piece of equipment or system at a time. Simultaneous cleaning demands result in scheduling conflicts and possible purified water shortages.

The problem of scheduling operations is not new, especially in industries where capital is at a premium and optimal use of available facilities is critical to survival. Some companies use industry standard scheduling tools such as MFG/PRO from QAD, (Carpinteria, CA) a provider of manufacturing software. However, these products may not have the features that address the particular nuances of biopharmaceutical operations.

Scheduling tools are now being added to process simulation offerings specifically for the biotechnology industry. Intelligen, the makers of SuperPro Designer (SPD), has recently released a scheduling software package, SchedulePro. Although SchedulePro is a stand-alone application, independent of SPD, models can be developed first in SPD and then exported to SchedulePro.

Aspen Technology expanded its original simulator and now includes a complete Manufacturing Execution System (MES). This solution includes site planning and scheduling, work order management, execution and analysis.

As with all of the simulation software tools, there is a price/performance decision to be made when deciding which tool to use. Often satisfactory simulation can be achieved with moderately priced packages in the hands of an experienced team.

Profiling Multiproduct Facilities

SuperPro Designer and SchedulePro are used here to illustrate some of the issues confronting a multiproduct facility. In this case, a somewhat simplified situation is presented to illustrate one possible approach to schedule optimization.

A flowsheet for the fermentation train of a biopharmaceutical manufacturing process is simulated using SuperPro Designer (Figure 1). The process includes two fermenters and associated media preparation. This is supported by one clean-in-place system and one steam-in-place system. The facility also accommodates a parallel identical process train manufacturing a different product.

Two identical flowsheets are created to model the facility with the two separate fermentation trains identified as Process A and Process B. The fermenters and the media storage tanks used in these processes are assumed different for the different trains; however, the media prep tank, V-103 is shared by the two trains. The utilities are also common to both processes: a CIP system (X-630-CIP) and a Steam-in-place (SIP) system(X-800-SIP)

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Based on the process and utility information provided to it, SchedulePro generated equipment occupancy profiles for the overall production schedule of a production campaign of two batches for each of the two fermentation trains. The resulting profiles chart is shown in Figure 2. Note that SchedulePro offset the start times for the batches so that there are no conflicts with using the shared skids or the shared media prep tank.

The resource profile for USP water consumption is shown in Figure 3. The larger peaks reflect the heavy use of USP water during CIP operations. This analysis is helpful in evaluating the capacity of the facility's USP system when called on to support multiple parallel production trains

Applying Process Simulation – A Team Approach

Applying process modeling effectively can initially involve a steep learning curve. Simulation software projects are often conducted by people who are experienced at using their particular software package but may know little about the actual operations they are programming or the significance of decisions they make about the operations. The combination of experienced programmers with experienced bioprocess designers or operators is an ideal approach to making a simulation truly useful and meaningful. To achieve the best results, Chemsim has previously combined with BioMetics experienced bioprocess designers, to generate meaningful, useful simulation models.

In summary, simulation is best applied to tackle complex problems where solutions are not obvious and where the investment is justifiable. For today's bioprocesses, those problems mostly arise from the design and operation of multi-product batch facilities. For example, being able to use an existing fermentation train to produce a second product therefore eliminating the need to add a new major fermentation production line with support systems could mean a huge savings ($20 to $50 million per line).

When recommending process simulators, there is no single correct answer. In the chemical industry, it is not unusual for a company to have every process simulator available, as they each have their strong points. Simulation software packages come in a range of prices. The key decision is to determine which one offers the best price/performance for the particular situation.

A very important area for simulation is the effective scheduling of multi-product facilities. Such scheduling/resource problems very quickly become highly complex in constrained, batch, multi-product systems with multiple production steps. A program with the capabilities of SchedulePro in the hands of a multidisciplinary team with the appropriate training and experience (programmers and process engineers) becomes a very powerful tool. This allows, for example, a contract manufacturer to maximize the utilization and thus the revenue of a facility - or allow a multi-product facility manager to investigate the effect of adding a new process/product on top of existing operations.

Fig 1. General Flowsheet for Process A and Process B

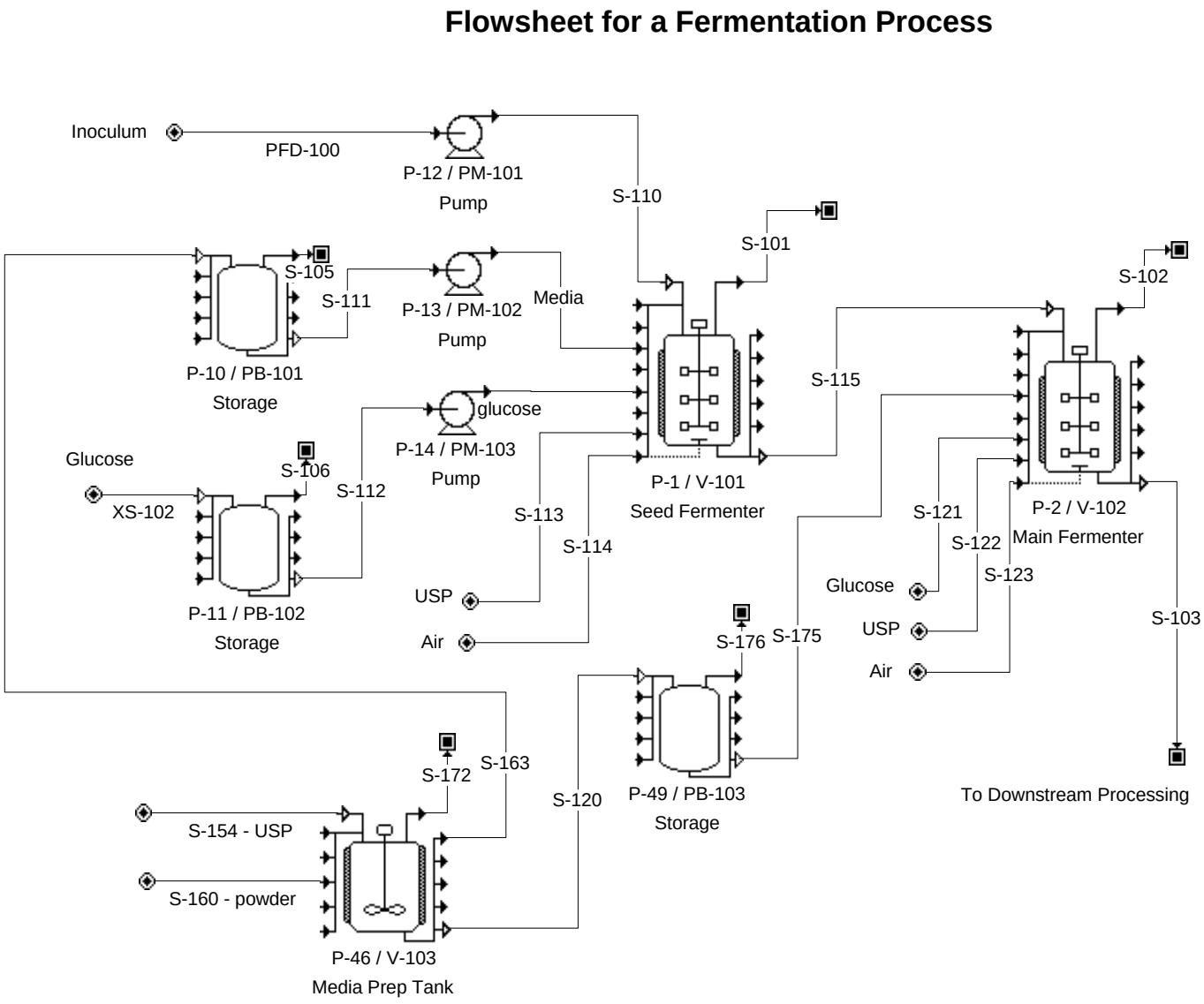

Fig 2. Equipment Occupancy Profiles for the Production Schedule

Legend:
B-0 - Process A, batch 1
B-1 - Process A, batch 2
B-2 - Process B, batch 1
B-3 - Process B, batch 2

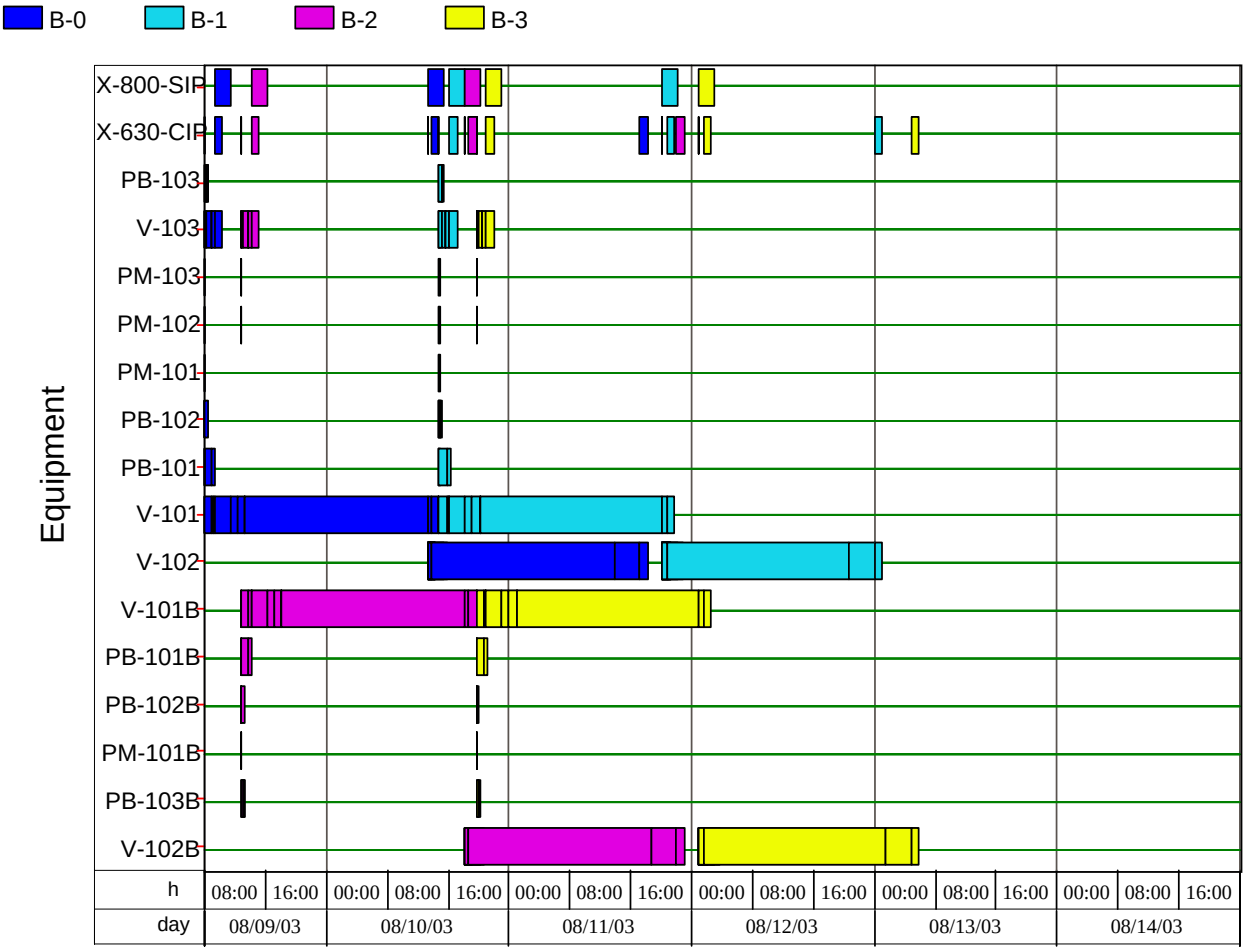

Fig 3. USP Resource Profile for Two Batches of Two Different Products – optimized schedule