Bioprocess Simulation: Taking the Error out of Trial-and-Error

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With the availability of simulation tools specifically designed for the biopharmaceutical industry, there is no excuse for not using them in the optimisation of bioprocesses.

Process simulation and modelling involves the application of a range of software tools to analyse individual unit operations (or process stages) and their relationships within the overall process. Process models are used to track material flows throughout the facility, to determine energy consumption, and to assess resource and utility requirements. This article reviews the tools available for the simulation of biopharmaceutical processes and how they can be applied in various manufacturing situations.

RESOURCE MANAGEMENT

In large, stainless steel-based biopharmaceutical facilities, the most important resources to manage are shared resources – such as labour, clean-in-place (CIP) skids, buffer tanks and media make-up tanks. It is important to consider utility requirements – such as electricity, steam, gas and water – but the most important utility to track is one associated with water, namely purified water and water for injection (WFI). The production of WFI requires both water and energy, and needs to be managed in such a way that sufficient volume is available for cleaning operations as well as process volumes.

In newer facilities that are focused on single-use technology, there is a different requirement for resource management. Here, the emphasis is on the management of labour as the operations are more labour-intensive, requiring more manipulations. Also, there is a shift in focus from utilities to the supply chain for procurement, storage, handling and staging of disposables, and the disposal of bags, containers and peripherals.

With ever-increasing cost pressures on the biopharmaceutical industry, there is currently an emphasis on production throughput and optimum use of facilities. Demanding questions arise from the increasing use of flexible multi-product facilities and contract manufacturing. Methods are required to allocate resources and utilities effectively and economically for competing parallel processes. The application of process simulation to maximise the utilisation of resource-constrained multi-product facilities can therefore yield profound economic benefits for companies.

For new, high-titer processes being fitted into existing facilities, questions arise with regard to equipment size, process throughput and equipment configuration. For example, high-titer fermentations often require a fed-batch scheme and this may require extra media feed-tanks to be procured and installed. The number, size and configuration of such tanks represents the first part of the upgrade process.

If a process has been running through a facility for an extended period of time, the individual batch operations will probably have been well optimised by an evolutionary process of continuous small changes. However, if there is a need to increase the run rate, then the way in which preceding and following batches interact with the current batch is not intuitive. In such cases, process simulation tools can be used to identify potential conflicts and bottlenecks.

MODELLING TOOLS

In spite of dedicated software packages targeted at process simulation, the premier tool for performing any kind of numerical analysis is still the spreadsheet. So today the largest supplier of simulation software tools is Microsoft, which offers several basic software tools that can be used for simulation:

- Excel® – Process calculations can be performed with spreadsheets and then reported graphically
- Visio® – Flow sheets can be constructed with a drawing package
- Project® – Process schedules and labour assignments can be produced

The advantage of using these tools is that many people are familiar with them and they are available on nearly all desktops; the disadvantage is that they were not designed specifically for bioprocess simulation. As a consequence, simulations using Excel, for example, often result in rather large and unwieldy spreadsheets that are difficult to maintain and document.

For a simple material-balance situation with just a few operations, a spreadsheet may suffice. However, using a

spreadsheet for the simulation of multi-product, resource-constrained facilities can become extremely time-consuming and error-prone. There are several commercial process simulation software packages available on the market but, 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. Some examples include the following:

- Intelligen's SuperPro Designer combines the drawing, calculation and scheduling features of the three Microsoft packages listed above into a single, moderately priced package, and offers a database feature to log equipment and utility capacities. The package also has the added advantage that it was specifically developed for the simulation of bioprocess unit operations and processes; it is user-friendly and set up to capture the unique unit operational data requirements of biological processes. Intelligen combines SuperPro with a scheduling package, SchedulePro, which is designed for facility modeling where there are multiple processes, or recipes, using a pool of resources.
- Aspen Technology, creator of the popular Aspen Plus for chemical processes, originally created a dedicated bioprocess simulator (BPS), which was eventually phased out and replaced by Batch Plus, a recipe-driven modelling environment for batch processes. The latest suite from Aspen Technology, AspenOne, includes tools for supply chain management in addition to advanced scheduling.
- Biopharm Services offers an Excel-based tool, Biosolve, which can be used for cost estimation and initial process design.

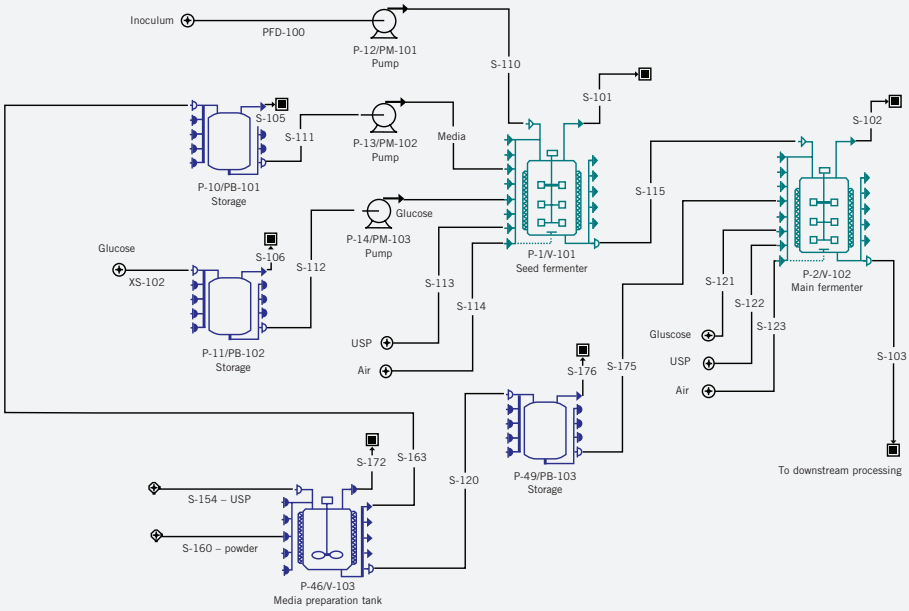
DISCRETE EVENT SIMULATION

To operate a multi-product, contract-manufacturing facility where processes are run in parallel requires a large degree of overlap between batches, and effective utilisation of shared resources and equipment. In fact the complex batch, multi-process, constrained optimisation problem is becoming one of the most important issues in the design and operation of biotechnology facilities. This is especially true for older facilities that are being re-configured for smaller, more frequent batches – a direct result of higher titer processes.

One approach to determining process schedules is by the application of discrete event simulation. This is appropriate where there are shared resources that do not have a defined schedule, but there is some flexibility as to when operations can be performed. Operations can occur within windows. For example in biologics manufacturing, purified water is used in significant quantities and is often a limiting resource – especially when multiple parallel cleaning operations are required. CIP systems usually clean one piece of equipment or system at a time. Simultaneous cleaning demands result in scheduling conflicts and possible shortages of purified water.

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 for this, such as

Figure 1: General flowsheet for Process A and Process B



MFG/PRO from QAD, ProModel, Infor (formerly Agilisys) and Extend.

Such tools create a Gannt chart of operations and can be tracked and logged. If there is an equipment malfunction, then the schedule can be re-computed. All the tasks can be reported and tracked. Being generic tools, they must then be customised to fit a particular process. Typically, the facility models are constructed by the software supplier on a consulting basis. There is little underlying support for particular industries.

Other discrete event simulation tools that are more focused on biopharmaceutical operations are Bio-G and BioSim. Although both of these tools are more focused on biopharmaceutical processes, a consulting effort is still required to set up the models. As run rates increase, room for manipulating the schedule decreases and the role of discrete event approaches diminishes. In this case, a good approach is SchedulePro.

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 optimisation.

A flow sheet for the fermentation train is first simulated using SuperPro Designer (see Figure 1). The process includes two fermenters and associated media preparation; this is also supported by one CIP system and one steam-in-place (SIP) system (not shown). The facility accommodates two parallel process trains manufacturing two different products. Two flow sheets are used to model the facility with the separate fermentation trains identified as Process A and Process B. Any equipment specific to train A and train B is uniquely named. Any shared equipment is identified with the same name. The shared CIP and SIP skids will not have unique names, as they are shared. Information from the two separate trains is then exported from SuperPro to the SchedulePro database.

Based on the process and utility information that was provided to it, SchedulePro generated profiles for the overall production schedule of a production campaign of two batches for each of the two fermentation trains. The SchedulePro offsets the start times for the batches so that there are no conflicts with using the shared skids or media prep tank.

A TEAM APPROACH

Applying process modelling 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 have little knowledge of the actual operations they are programming or the significance of decisions they make. The combination of experienced programmers with experienced bioprocess designers or operators is essential to making a simulation truly useful and meaningful.

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, these problems mostly arise from the design and operation of multi-product facilities, process fits for new processes and the design of new single-use facilities. For example, being able to use an existing fermentation train to produce a second product – thereby eliminating the need to add a new major fermentation production line with support systems – could mean 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 each has its own 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.

The first generation of bioprocess simulation tools were adapted from simulators used in the chemical industry and were not too useful for biopharmaceutical processes. Today, the situation is very different and currently available tools should now form an integral part of any bioprocess design and optimisation study.

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