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THE ROLE OF PROCESS SIMULATION AND SCHEDULING TOOLS IN THE DEVELOPMENT AND MANUFACTURING OF BIOPHARMACEUTICALS

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ABSTRACT

Pharmaceutical manufacturers generally employ either organic synthesis or biotechnology. Each of these technologies has unique challenges, but batch process simulation and scheduling tools can facilitate process development in both. Batch process simulation is distinct from both traditional chemical process simulation and dynamic simulation and is uniquely suited to pharmaceutical processes. Furthermore, there is a close relationship between the data required for batch simulation and the data required for batch process scheduling. An example biopharmaceutical process illustrates how batch simulation can help improve a process. A scheduling example illustrates the relationship between batch simulation and scheduling.

1 INTRODUCTION

1.1 Motivation

The commercialization of a new drug takes 7 to 12 years to complete and requires investments ranging from $100 million to $800 million and with 80 to 85% of products failing somewhere in the development pipeline (Polastro 1996, Petrides et al. 1999). Process development and design usually contribute a small fraction of the overall cost and are rarely on the critical path. This, however, is bound to change. As chemicals become increasingly complex and competition puts more pressure on profit margins, companies will realize the importance of developing novel processes, decreasing production costs, increasing efficiency and doing the design right from the start to avoid the significant costs associated with making process changes later on.

Computer-aided process design (CAPD), simulation, and scheduling tools can improve pharmaceutical process development while helping to keep it off the critical path to drug commercialization. Their most important advantage is that they allow fast, inexpensive and easily to document experimentation with numerous process alternatives that would be difficult to evaluate by hand calculations or experimentally. Computer models can, for example, pinpoint the economic "hot-spots" of a complex process, i.e. the steps of high capital and operating cost or low yield throughput, or identify the environmental hot-spots such as solvents and regulated materials that are costly to treat. The findings from such analyses can be used to judiciously focus further lab and pilot plant studies, reducing development time and cost.

The benefits from the use of CAPD tools extend beyond process development to all stages of the commercialization process. Process models can facilitate technology transfer. A computer model of the entire process constitutes a common reference and evaluation framework for all developers and can facilitate team interaction by providing a common language of communication.

1.2 Batch Process Simulation

Chemical process simulation tools became commercially available in the 1980's. These programs were developed to model continuous plants.

Theses programs employ the concepts of the unit operation library and the component library. A unit-operation model contains the engineering calculations that relate the equipment and material properties to material and energy flows around a process unit, e.g. a reactor. The component library contains the material physical property data required by the unit operation models, e.g. densities and boiling points. Process models usually consist of several unit operations and the flows that connect them. The simulator calculates average values for flows, temperatures, pressures, and material compositions in the plant. Batch units can be accommodated by using an average flow rate calculated as the process volume divided by the overall process duration.

This averaging technique only reflects reality if there is storage between the batch operations and if batch integrity is not required. Neither of these assumptions apply to biopharmaceutical processes.

Dynamic simulators and differential equation solvers can provide instantaneous, rather than average values but are cumbersome and do not provide useful process libraries.

The 1990's saw the development of three batch process simulators: Batch Plus from Aspen Technology, Inc.,

Batch Design Kit from Hyprotech, Ltd., and SuperPro Designer (SPD) from Intelligen, Inc. SPD has its roots in BioPro Designer, a novel tool that was developed at MIT in the late 1980's to address the needs of the biopharmaceutical industries. Although, there are many similarities among the batch simulators mentioned above, they each have unique features. The remarks that follow are based solely on experience with SPD.

The batch simulator maintains the advantage of the library of models but also accounts for batch timing. The concept of a unit-operation is expanded to a *unit-procedure* that consists of a series of operations as shown in Figure 1.

Unit Procedure: Reaction (in R-101)
Operation: Charge materials
Operation: Agitate / React
Operation: Cool Down
Operation: Transfer out
Operation: Clean reactor

Figure 1: Sample Unit Procedure Model

Each operation requires process information and scheduling information. Process information consists of the amount and composition of the material being handled along with specific operating conditions associated with the equipment.

SPD expresses scheduling information in terms of operation duration and operation start-time. An operation's duration may have one of the following forms:

- Fixed by the user
- Calculated based on the appropriate engineering model
- Fixed by the duration other operation(s).

Furthermore, an operation's start may be set by one of the following time markers:

- Fixed by the start of the batch
- Fixed to the start of another operation
- Fixed to the end of another operation.

SPD solves the material, energy, equipment sizing and duration calculations for each operation independently of the start-time calculations. This technique relies on the notion that operations in batch processes proceed with discrete transfers of material from one operation to the next. These calculations fix the operation durations. SPD then uses the operation start-time relationships to set up the relative timing of all the operations. Finally, SPD optionally runs the economic calculations.

1.3 Relationship to Scheduling

Batch simulators maintain much of the data necessary for batch process scheduling. In particular, scheduling programs require the operation durations and the scheduling relationships. SPD can export this scheduling information in an open database format.

2 SIMULATING A BIOPHARMACEUTICAL PROCESS

2.1 Developing the Model

SPD is a flowsheet-driven application. The user enters the process flowsheet by putting together unit procedures (or simply procedures, for short) selected from the SPD library.

The flowsheet in Figure 2 represents a batch process for the production of a therapeutic monoclonal antibody. The process entails a series of cell culture steps to grow cells to a sufficient concentration for the large scale bioreactor. In the bioreactor, the cells generate the product along with a variety of impurities. The remaining procedures are a sequence of purification and concentration steps.

The process model contains the following types of procedure models from the SPD library:

- Bioreactors (T-Flask, roller bottle, disposable, seed fermentor, and stirred vessel)
- Dead-end filtration
- Agitated tank mixing
- Centrifugation
- Ultrafiltration/Diafiltration
- Chromatography.

The lines connecting procedure icons represent batch material transfers from one process step to another.

To complete the model, the user enters information about the materials to be processed. Material physical properties may be read from the component database or entered manually. For each procedure, the user sets up the operation sequence, e.g. "charge materials", "heat", "transfer", etc. Finally, the user initializes each operation with the appropriate engineering data, e.g. charge quantities, reaction stoichiometries and scheduling relations.

The user may organize the flowsheet in different sections. Figure 2 shows boxed titles for each section.

The grouping of procedures in sections allows for different considerations (such as economic data) to apply to each section.

2.2 Simulation Results

The solution of material and energy balances involves the calculation of the flowrate, composition and thermodynamic state of all streams and equipment contents in the flowsheet. The user may view the results through the streams, through a stream table that can appended to the flowsheet or through a comprehensive stream report that SPD generates on demand. For example, Table 1 shows the calculated raw material requirements.

Monoclonal Antibody Production

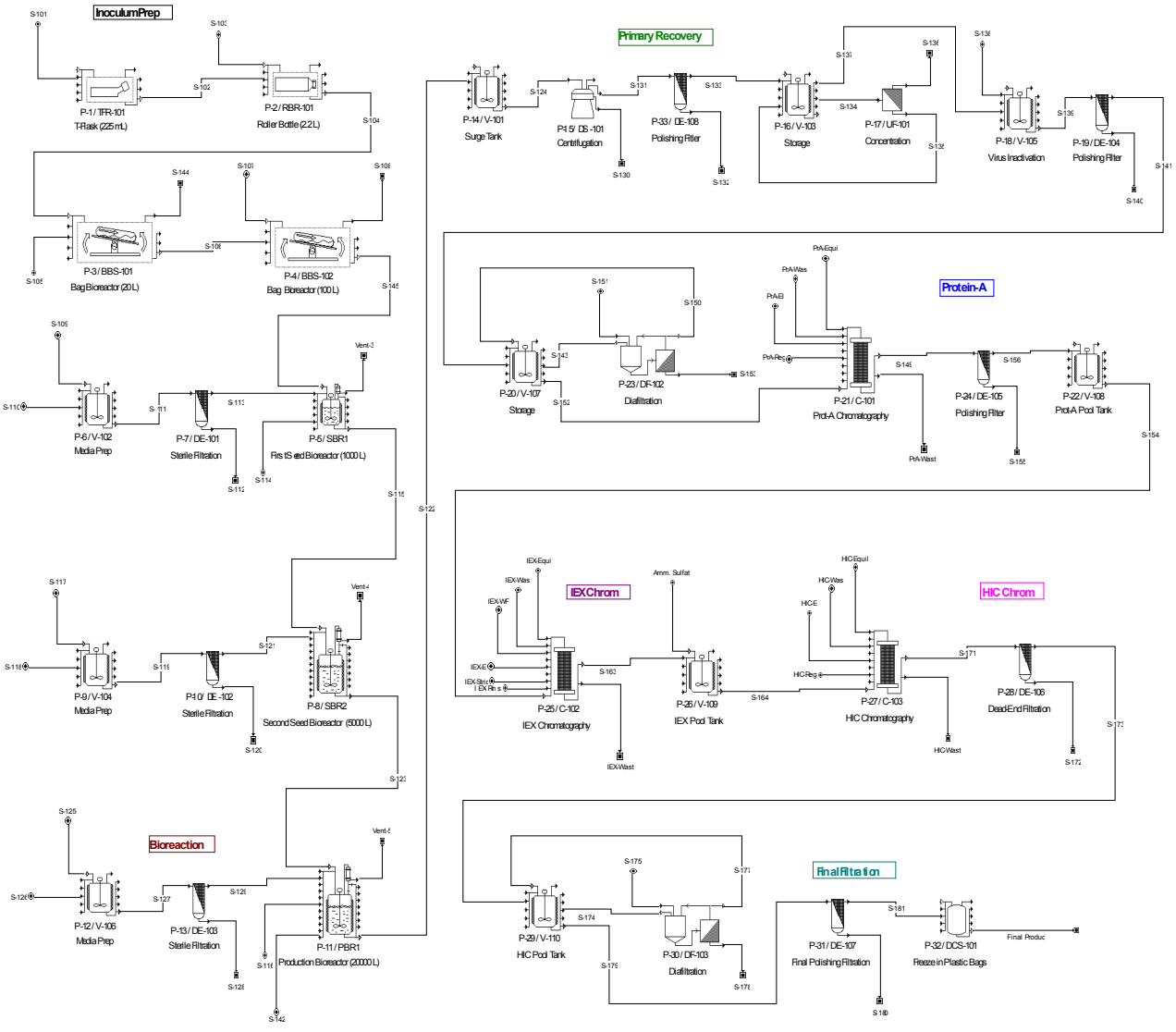

Figure 2: Monoclonal Antibody Process

As part of the material balances, SPD also computes emissions and the environmental load of all streams so that the environmental impact of the process can be assessed.

2.3 Equipment Sizing

SPD calculates the size of all equipment in the flowsheet that are in 'design-mode'. When equipment is shared among different procedures, the equipment is sized to satisfy the most demanding procedure. If the equipment is in 'rating-mode', i.e. the user defines its size and SPD checks the feasibility of carrying out the assigned procedures to that equipment.

2.4 Cycle Time Analysis

Using information on the sequence of tasks and calculated execution times, SPD schedules one execution the entire process, i.e. one batch. SPD then checks the feasibility of executing the recipe in time. The user may display results in Gantt charts or equipment utilization charts as shown in Figure 3.

Equipment is assumed to be unavailable for other batches from the time it is first used until the time it is last released. If equipment is not re-used in a process, the unavailability of an equipment unit corresponds to the duration of the procedure that uses it. If equipment is reused, the unavailability corresponds to the total duration of the processes that use the equipment plus the idle time between

Table 1: Raw Material Requirements

Raw Material	kg/batch	kg/kg prod
Inoc Media Sltn	59.2	2.3
WFI	56,727	2,250.
Media	17.4	0.692
Air	24,675	978
SerumFree Media	822	33
RO Water	33,587	1,331.
NaOH (0.5 M)	45,374	1,799
Acetic-Acid	15.526	0.616
Prot-A Wash Buf	10,377	411
Prot-A Reg Buff	8,648	343
IEX-Eq-Buff	7,814	310
IEX-Wash-Buff	7,822	310.
IEX-El-Buff	440	17.4
NaCI (1 M)	4,810	191
Amm. Sulfate	348	13.6
HIC-Eq-Buff	2,970	117
HIC-Wash-Buff	7,425	294
HIC-El-Buff	7,180	284
PBS	1,427	56.6
TOTAL	220,540	8,746

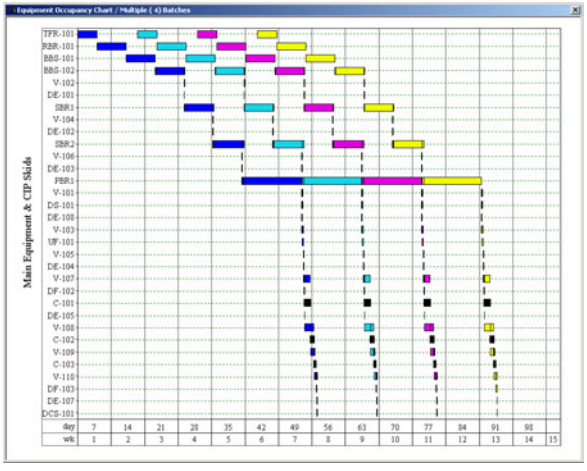

Figure 3: Four Consecutive Batches Colored by Batch

usages. The longest period of unavailability becomes the process cycle time, i.e. the minimum time between consecutive batch starts. The equipment with the longest unavailability is the scheduling bottleneck (PBR1 in this example). The example process has a cycle time of 12.5 days.

The process drives the scheduling. For instance, an increase in batch size will increase the duration of operations such as charge, filtration etc. This, in turn increases the batch cycle time and decreases the maximum number of batches can be made.

2.5 Economics

SPD performs thorough cost analysis and project economic evaluation calculations. The fundamentals of process economics that SPD implements are described elsewhere (Harrison et al. 2003). Table 2 shows the key economic evaluation results as generated by SPD. With a selling price of $200/g, the project yields an after-tax internal rate of return (IRR) of 70% and a net present value (NPV) of $31.4M. Manufacturing costs, of course, represent only part of the cost of biopharmaceuticals. SPD also allows the user to add other cost elements, such as up-front R&D. If we charge $50M of R&D to the project, the IRR drops to 35%.

Table 2: Economic Summary

Total Capital Investment	$53,646,000
Operating Cost	$36,532,000/yr
Production Rate	580 kg/yr
Unit Production Cost	$63 /g
Total Revenues	$115,997,000
Gross Margin	68 %
Return On Investment	98 %
Payback Time	1.02
IRR (After Taxes)	70%
NPV (at 7.0% Interest)	314,334,000

The user may control the outcome of the economic calculations by overriding estimated values such as costs of equipment, utilities and raw materials, and providing economic input data at the section as well as the flowsheet level.

2.6 Example: Increasing Plant Productivity

In biopharmaceutical processes, engineers may often be faced with the challenge of optimizing a process without making any fundamental changes. Suppose, in this example, that good results from clinical trials indicate that additional process capacity is needed. Redesigning the bioreactor would be out of the question because it could have an unknown effect on the final product.

A quick examination of Figure 3 shows that most of the process time is associated the production bioreactor. All the other procedures are relatively fast. As a result the equipment is under-utilized. Therefore there may be some advantage in using two or more identical bioreactors alternately.

SPD provides an easy way evaluate this possibility. Each unit procedure may be assigned additional alternate (or staggered) equipment. SPD then re-evaluates the timing and economics assuming that for the first batch, the first alternate is used, and the second for the second batch, etc.

In the biopharmaceutical example, up to four bioreactors may be added as shown in Figure 4.

In this case, the batch one uses PBR1, batch two uses the alternate, STG 01 - PBR1. This strategy almost doubles the production rate. Of course, the increased rate comes at the price of an extra bioreactor. If the extra capacity is merely used to make the same number of batches in a shorter time, the unit cost increases to $64/g. If the increased capacity can be used to make additional product, the new production cost drops to $56/g.

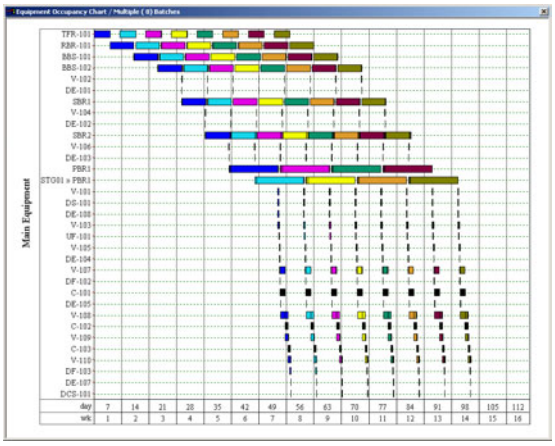

Figure 4: Two Bioreactors, 8 Batches

3 SCHEDULING ISSUES

3.1 Exporting Scheduling Data

Like many batch process simulation programs, SPD contains only some, of the data needed for process scheduling. SPD has operation durations and scheduling dependencies, but it does not have "real word" information, e.g. holiday and maintenance schedules, material shipments and receipts. The SPD strategy is to export the following data to an open database format:

- Unit Procedures: only the name and description are exported
- Main equipment for the procedure
- Operation durations
- Operation scheduling relationships
- Operation resources (extra equipment, labor, utilities and materials).

Each process exported from SPD becomes a recipe in the database.

3.2 Solving a Scheduling Problem

Batch simulation in SPD is based on a single batch analysis. That is, cycle-times are assumed to be constant from batch to batch, and every batch is assumed to have identical process durations. While this analysis is appropriate for process design and de-bottlenecking, , it can be unrealistic for production scheduling.

For example, a common issue in biopharmaceutical processes is the variability of cell culture times. A production planner might want to know what would happen to the schedule if a production bioreactor run were to take a day longer than expected.

In fact, SPD is not the best tool to answer this question. SPD does not handle either variable batch times or the completion status of operations. Resource-constrained scheduling tools can manage these requirements, and SPD's recipe export capability reduces the effort of setting up the scheduling problem.

The solution is to export the process recipe from SPD to a database format and import the recipe in SchedulePro – a resource constrained scheduling program from Intelligen, Inc. SchedulePro allows for both completion tracking and batch-to-batch variation. Within SchedulePro, the user may add a "safe hold," i.e. a point at which the process may be delayed without adversely affecting the product.

In this case, a one-day delay has an impact on the schedule as shown in Figure 5. At the time of the delay, three batches are in progress. The second batch is not affected because it uses the alternate bioreactor. The delay does, however, affect the third batch because the production bioreactor is still busy with the first batch. SchedulePro uses safe hold, which was introduced at the start of P-8 in SBR2, to delay the start of the second seed bioreactor. This delay allows enough time for the first batch to finish with the main bioreactor (PBR1) before the third batch needs it.

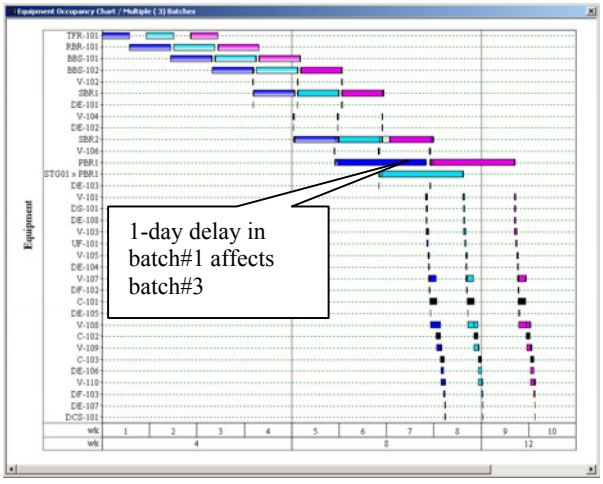

Figure 5: Three Batches with a 1-Day Delay in Batch 1

4 CONCLUSIONS

Batch process simulators such as SPD, provide the calculations required to analyze, de-bottleneck and optimize batch processes without the need to resort to full dynamic simulation. These tools can also be the framework to communicate, and document process changes, to transfer or scale-up technology.

Resource-constrained scheduling tools such as SchedulePro, can simulate the effects of time-varying constraints and batch-to-batch variations. Because batch simulation models contain the recipe information needed for scheduling, an open data transfer between the two systems eliminates the time and effort of setting up a scheduling model.

More and more batch industries enjoy the benefits from the use of CAPD tools and this trend is bound to strengthen as, increasingly, engineering schools incorpo-

rate batch process material and simulation in their curriculum. In the future, we can expect to see increased use of this technology and integration with other enabling technologies, such as batch process control and manufacturing execution systems. The result will be more robust and efficient processes, developed faster and at a lower cost, making higher quality products.

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