

Optimization of Biopharmaceutical Manufacturing with Scheduling Tools - Experiences from the Real World

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Abstract

This paper presents industrial experience with a resource-constrained batch process scheduling program. The batch process representation is loosely based on the ISA S88 batch process standard. This representation allows the import of batch process information from other software, e.g. batch process simulators. The scheduling algorithm is a non-optimization approach that proceeds in two steps. First a bottleneck analysis is done to determine a lower bound on the process cycle time, and all the batches are scheduled accordingly. Second, if conflicts remain, they are resolved by applying progressively aggressive modifications to the schedule.

This approach to scheduling was tested on several biotech processes. These processes consist of a sequence of batch steps performed with dedicated equipment. The scheduling challenges in biotech processes lie in the ancillary operations: media and buffer preparation, vessel and line cleaning, and chromatography column preparation. Such operations may use shared resources and may serve to couple process suites with otherwise dedicated equipment. These considerations are further complicated by variability in process durations.

Three case studies, which are based on a process for the manufacture of monoclonal antibodies (MABs), illustrate the value of a constrained-resource scheduling tool for biotech processes. In the first case study, the scheduling tool shows that auxiliary cleaning equipment can limit batch production. A second case study shows how scheduling tools can calculate the size of a purified water system. A third case study illustrates how to use scheduling tools to mitigate the effects of process variability.

Keywords: scheduling, process modelling, biotech, pharmaceutical manufacture

1. Introduction

Biotechnology manufacturing capacity is currently in very high demand. In recent years the estimated capacity utilization has been 90% for both microbial and mammalian cell culture production (S. Fox et al., 2001). Some biotech firms have estimated potential revenue losses of well over \$100 million due to lack of

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manufacturing capacity (R. Rouhi, 2002). Thus there is substantial motivation to improve process efficiency in biotechnology manufacturing.

1.1 Bioprocessing Overview

A typical biopharmaceutical process consists of two parts: an upstream process in which a living organism produces the product in a raw form and a downstream process in which the product is purified. Most biotech upstream processes employ either microbial fermentation or mammalian cell culture. From a scheduling viewpoint, biotechnology processes generally have the following features:

- They are batch processes
- Primary processing equipment is dedicated to a particular processing step
- Wait-time between process steps is either zero or limited
- From 20 to 30 buffers may be made for each batch and each has a limited life
- There is some variability in processing times especially in the upstream processes
- Equipment cleaning is common after most process steps and often requires auxiliary clean-in-place (CIP) skids, which are not dedicated

Biopharmaceutical manufacture is regulated, and manufacturers need to prove, through studies or clinical trials, that a process change will not adversely affect the product. Manufacturers therefore tend to avoid any direct changes in the process itself.

1.2 Scheduling Challenges

For most bioprocesses, scheduling the main process does not pose a significant challenge. Because the steps usually proceed with no wait, the timing is fixed when the batch start is fixed. Scheduling challenges arise in the support operations such as cleaning and buffer preparation. Such support operations may impose unexpected limits on the process. Common utilities, such as purified water, may impose scheduling limits because they impose limits on both peak and average resource consumption. Finally, planning for process variability and failures presents a significant challenge.

2. A Scheduling Tool for Bioprocessing

Most bioprocess manufacturers employ spreadsheets for process scheduling because spreadsheets are inexpensive, readily available, easy to learn and highly flexible. For more complicated situations, however, spreadsheets have very clear drawbacks including poor visualization tools and poor maintainability. Furthermore, spreadsheet solutions are usually “owned” by an individual and may be difficult to transfer to another individual or to another site.

The scheduling tool and approach described in this section maintains many of the advantages of the spreadsheet approach while minimizing the disadvantages.

Pekny and Reklaitis (1998) describe a generic scheduling tool consisting of graphical user interface, a representation layer, and problem formulation and solution layers.

2.1 The Interface

The interface should provide both an easy means of entering and maintaining scheduling information and appropriate displays of the scheduling outputs. The equipment occupancy chart is the most popular way to display scheduling information

for bioprocesses. Equipment occupancy charts, as shown in Figure 5, display Gantt-style time-bars for equipment.

2.2 The Representation Layer

The representation consists of a model for the process and its associated resources and constraints. The instructions for making a single batch of a product constitute a recipe. The recipe structure, which is loosely based on the ISA SP88 standard, consists of unit procedures and operations. A unit procedure is a primary process step and is assigned a single unit of primary equipment. Operations are individual tasks within a unit procedure. All resources other than primary equipment, i.e. auxiliary equipment, labor, materials and utilities, are associated with operations.

Operation durations may be fixed or rate and/or equipment dependent. Rate dependent durations are linearly dependent on the batch size. Scheduling precedence relationships exist among operations. Specifically, an operation may have any of the following timing dependencies: (1) the operation starts at the beginning of the batch, (2) the operation starts simultaneously with a reference operation, (3) the operation starts at the end of a reference operation or (4) operation finishes at the start of a reference operation.

In addition to the relationships above, an operation may have a fixed or flexible shift time. A fixed shift indicates the time after (or before) which the dependency condition is fulfilled that the operation actually starts. A flexible shift indicates the maximum time that an operation may be delayed.

2.3 The Formulation and Solution Layers

There is an abundance of proposed problem formulations and solution algorithms for scheduling problems. The goal of the scheduling methodology described below is to allow a user to generate and evaluate a schedule interactively.

The user enters a plan with one or more campaigns each of which consists of a number of batches of a particular recipe and either the due date or start date. The system lays out a preliminary schedule using the cycle-time analysis and conflict resolution methodology. The user may edit the resulting schedule.

The system schedules a campaign by scheduling batch starts according to the estimated cycle time. The cycle time for a recipe is the average time between consecutive batch starts. The minimum cycle time, T_{cycle} , is estimated by the following relation from Biegler et al. (1997).

$$T_{cycle} = \text{Max}(T_i/N_i) \text{ for } i = (1, M) \quad (1)$$

T_i is the duration of unit procedure i , N_i is the number of alternative primary equipment units, and M is the number of unit procedures. This estimate does not account for shared primary equipment, auxiliary equipment, or down-time, so a conflict resolution scheme is employed to ensure that the resulting schedule is feasible. Conflicts are resolved by (1) selecting other equipment, (2) adding a flexible delay, or (3) delaying the start of a batch.

3. Bioprocessing Case Studies

The case studies draw on a process for producing a monoclonal antibody product. The process, shown in Figure 1, consists of multiple upstream suites and a single

downstream suite, which is detailed in Figure 2. The upstream process is limited by the production bioreactor, which has a processing time of 12 days. Multiple upstream suites allow for a batch every 48 hours, while the downstream suite has a minimum cycle time of 33 hours. The limiting equipment in the downstream process is the buffer hold vessel, DCS-103.

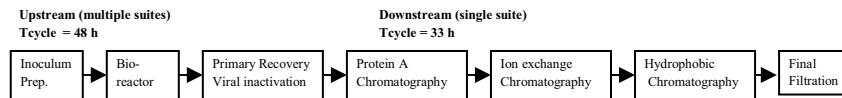


Figure 1. Monoclonal Antibody Process

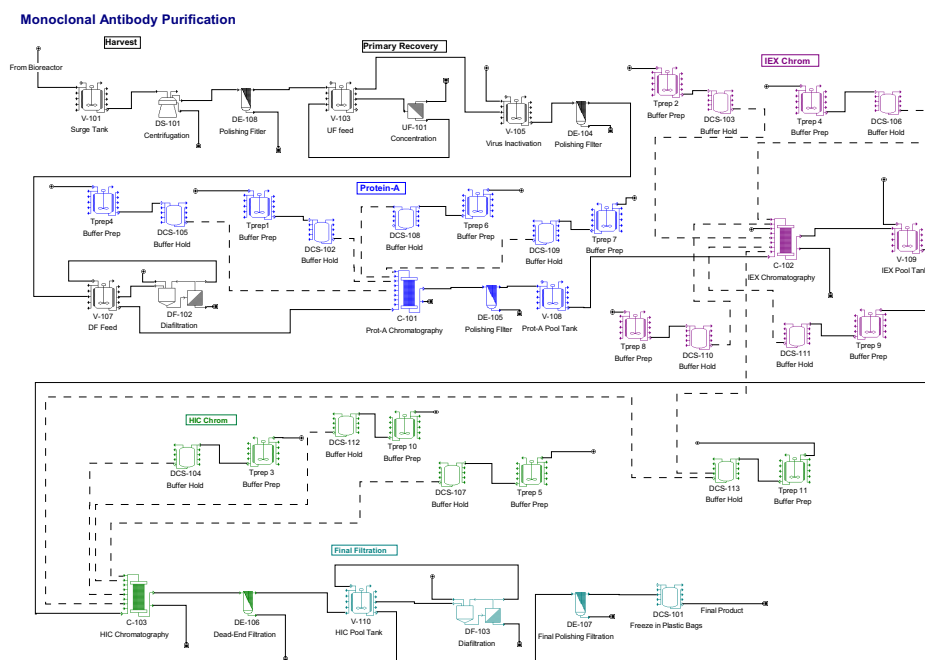


Figure2. MAB Downstream Details

3.1 Case Study 1 CIP Skids

The objective is to schedule the downstream process to accommodate upstream improvements that would reduce the upstream cycle time to 36 hours.

When the system is given a target cycle time of 36 hours, it reports that the process may not be scheduled. In fact target cycle times of 46, 36 and 35 hours aren't met. Target cycle times of 48, 45, and 34 hours, however, are achieved. The equipment occupancy chart in Figure 3 reveals the problem. CIP-SKID-1 is conflicting from batch to batch. The cleaning skid is used to clean the bioreactor harvest tank, V-101 and is required at the same time to clean the IEX elution buffer tank in the second batch, so the second batch is delayed at the expense of the cycle-time target.

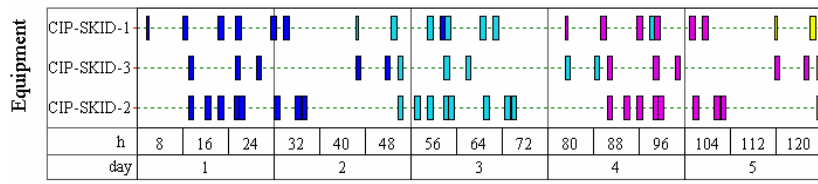


Figure 3. CIP Skid Usage (Color Coded by Batch)

The key to resolving the problem lies in understanding where to add flexibility. While a delay in a step that affects the product would probably not be allowable in a biopharmaceutical process, a short delay in cleaning a vessel would be acceptable. In this example, a delay of up to 2 hours before cleaning the buffer tanks allows any cycle-time target greater 33 hours.

3.2 Case Study 2 Estimating Water for Injection Requirements

Purified water known as water for injection (WFI) is used extensively in bioprocesses both for the process and for cleaning vessels. A WFI system consists of a still, surge tank and circulation system. The still capacity surge vessel requirements are dependent on the production schedule.

A plot of WFI consumption, shown in Figure 4, gives the basic design parameters. Under peak conditions a four-hour WFI turnover is chosen. The plot shows the instantaneous consumption (light red), the 4-hour average consumption rate (dark blue) and the 4-hour cumulative consumption (brown). The approximate still capacity can be set to peak average rate (9,000 L/h) and the vessel size to the peak 4-hour consumption (35,000 L).

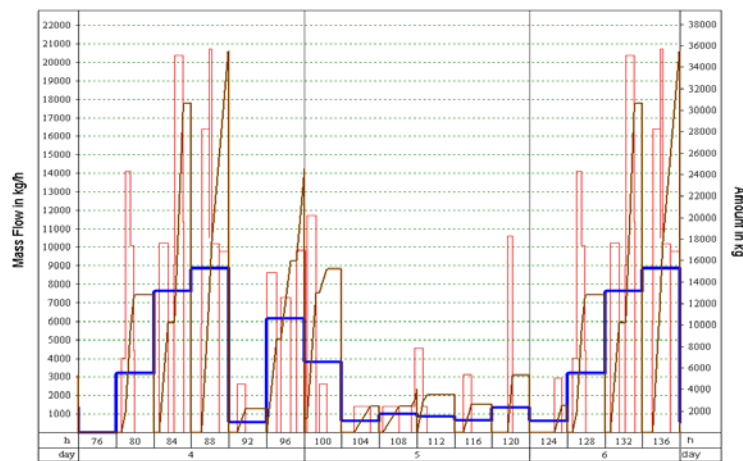


Figure 4. WFI Consumption

3.3 Case Study 3, Scheduling for Uncertainty

An important source of uncertainty in bioprocesses arises from variability in bioreactor durations combined with the long processing times. In the MAB process above, the completion time of an upstream batch may easily vary by a day.

An analysis of the cycle time shows that a 24-hour delay in the upstream process will cause a conflict in the downstream schedule. The upstream cycle time is 48 hours, and the downstream cycle time is 33 hours. A 24 hour delay in the upstream process reduces the time between consecutive branches as follows: $(48\text{h} - 24\text{h}) < 33\text{h}$.

As noted earlier, the cycle-time limiting procedure is a buffer hold step. Buffers are normally made up about a day in advance and held. See the DCS equipment in the first batch in Figure 5. In an emergency, buffer preparation could reasonably be delayed as long as the buffers are ready in time for the chromatography. The user interactively resets the start times for the buffer preparation steps in batch 3 and shifts the start of batch 2 by 24 hours as shown in Figure 5.

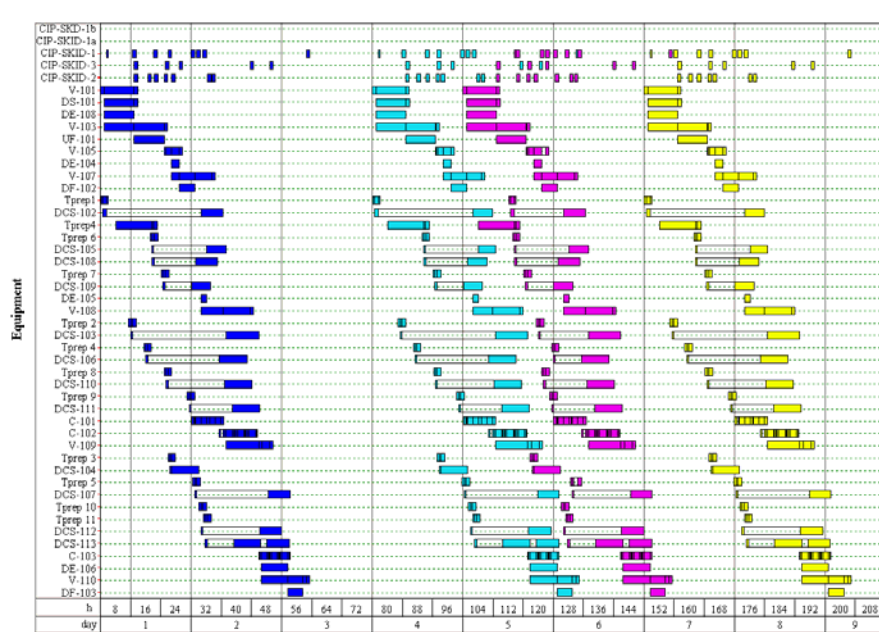


Figure 5. Schedule for a Delay in the Second Batch

4. Conclusion

For most bioprocesses, tight constraints dictate much of the scheduling. Under such conditions interactive scheduling tools can deliver a considerable benefit even if they do not generate mathematically optimized schedules.

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