17th European Symposium on Computer Aided Process Engineering – ESCAPE17
V. Plesu and P.S. Agachi (Editors)

Scheduling Challenges in Biopharmaceutical Manufacturing

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Abstract

For a scheduling tool to be acceptable and effective in biopharmaceutical manufacturing it must embrace the richness of constraints that exist in the biomanufacturing floor. It must also provide a way to quickly develop and modify feasible schedules. This paper discusses the unique challenges that characterize scheduling in biopharmaceutical manufacturing and sketches the features of a tool that can effectively meet these challenges.

Keywords: scheduling, biopharmaceutical manufacturing

1. Introduction

Scheduling production in multi-product batch biopharmaceutical facilities is a challenging and, in many respects, unique problem despite some similarities with other industrial fields (see, for example, [1] for scheduling issues in the food industry). Recipes are complex, involving many processing steps and even more support operations [2]. They use a large number of sharable media and buffer solutions that need to be prepared in advance but have limited lifetime. Variability in processing times (especially in the cell culture processes) and the constraint of zero or limited wait-time in between steps add to the scheduling complexity.
At the facility level, constraints arise from the facility layout or compatibility limitations between equipment. Inoculum preparation suites that selectively feed specific bioreactor trains are examples of constrained suite connectivity

within a facility. Scheduling conflicts also arise due to the competition between operations for the use of shared CIP (Clean-In-Place) skids for equipment and line cleaning, as well as the use of mobile tanks, transfer panels and delivery lines for material transfers. In biopharmaceutical manufacturing it is a well-known fact that bottlenecks very often arise in the use of auxiliary equipment.
The abundance and idiosyncratic nature of these constraints call for a very rich and customized representation of the recipes and the available resources before the scheduling problem can be attacked. On the other hand, feasible solutions that respect all constraints should be generated quickly and efficiently. This renders optimization-based approaches impractical for factory use. The features of a tool that aspires to meeting the biopharmaceutical scheduling challenges are sketched in this paper along with an illustrative example.

2. Representation Aspects

Setting up a scheduling problem includes the declaration of available resources, the recipes to be executed and a plan of product campaigns.

2.1. Resources

Resources used for the execution of process recipes are organized into *facilities*. A facility represents a grouping of resources that embodies their common attributes such as a calendar where downtimes and outages can be recorded. When a facility is down, all of its declared resources are unavailable.
The following types of resources may exist in a biopharmaceutical facility:

- Labor
- Utilities (heating, cooling, power)
- Equipment (main and auxiliary)
- Transfer/flow panels
- Work areas
- Storage units
- Material supply systems

This level of categorization of resource types is necessary not only because these types correspond to easily identifiable entities in a real biopharmaceutical facility, but also because they require different handling from the scheduling point of view. Equipment can have scheduled maintenance outages or unscheduled breakdowns, labor availability can fluctuate during the day or the week, materials can be delivered to or discharged from storage units at a continuous rate or at scheduled events. All resources are therefore equipped with calendars where all resource-specific events can be recorded.
Each resource type also contributes with its own unique constraints to the scheduling problem. Equipment can have capacity and/or processing rate limitations. Most equipment can only serve one process at a time but there are equipment units that can handle multiple processes simultaneously. Examples

are autoclaves, washers, freezers, heating pools and transfer panels. Transfer or flow panels are engaged (possibly more than one in sequence) in transferring material between unconnected equipment. These panels have a set of *ports* that can be selectively combined through a set of *bridges* or *jumpers*. By appropriately connecting available ports through bridges multiple simultaneous transfers are possible. The number of bridges imposes an upper bound on the number of simultaneous transfers but the achievable number of possible uses could be less depending on the compatibility of the remaining ports and bridges. Work areas represent facility resources such as laboratory rooms that are reserved for use while a recipe or a recipe step is executed.

Storage units exist in abundance in biomanufacturing. They supply raw materials to the process, accumulate products and waste or store intermediates. Biopharmaceutical facilities are also equipped with central supply systems for materials that have multiple uses in the plant. Purified water is such a material that can be used for equipment and line cleaning, steam generation or as ingredient in buffers. It is important that these supply systems are sized appropriately and their inventories followed during the scheduling horizon to ensure availability of materials whenever they are needed.

The representation of facility resources is not complete unless compatibility or connectivity constraints between them are declared. One way to represent such constraints is by organizing the resources in *suites*. Suites can be linked with other suites in a preferential way. Compatibility constraints between main and auxiliary equipment may also be present.

2.2. Recipes

The representation of recipes follows loosely the ISA S88 standard [3]. A process recipe consists of *sections*, *unit procedures* and *operations* organized in a nested hierarchy. A unit procedure is the primary process step that takes place in a single piece of equipment and consists of operations. The grouping of unit procedures in process sections allows the isolation of process steps that share common features such as their ‘preference’ to collectively reserve a common facility suite for their execution. The implication is that if a process ‘enters’ a suite, then all subsequent procedures in that section have to be executed in the same suite while, at the same time, no other process can use resources from that suite even if they are available. This is a common practice to avoid cross-contamination between different products or even between different batches or processing steps of the same product. Suite selection for subsequent processing sections is constrained by suite compatibility.

Unit procedures have a pool of candidate equipment (and, optionally, work areas) suitable for their execution. Further screening of equipment can result from imposing size limitations or reservation constraints (e.g. two or more procedures in a batch must use the same equipment, or, a procedure might reserve its equipment for exclusive use within the same batch).

Defining an operation within a procedure includes the specification of its duration and start-time. The operation duration can be fixed, rate-dependent or set equal to the duration of one or more 'master' operations so that simultaneous tasks can be modeled. An operation's start or end time may be set in relation to either the batch start or the start or end of another operation. Whenever applicable, an operation may be declared to have a fixed or flexible shift time so that its start time is free to move forward or backward in time with respect to its nominal scheduling reference. It can also be declared as interruptible so that its execution can be stopped and resumed at a later time. The scheduling tool exploits these flexibilities in the execution of an operation to overcome conflicts due to unavailability of resources.
Operations may require the use of additional facility resources beyond the main equipment used by the procedure they belong to. These include auxiliary equipment, transfer panels, labor, utilities, power and material resources that can be drawn from or deposited to storage units. As is the case for procedures, operations can select from a pool of resources to satisfy their processing needs.

2.3. Production plan

A production plan is declared through a set of *campaigns*. A campaign consists of a number of production batches of a given recipe along with any pre-production or post-production steps (e.g. equipment cleaning). Batches in a campaign are exact or scaled (with respect to batch size) instantiations of the master recipe. A user-provided ordering of campaigns can be used to assume their implicit prioritization. Alternatively, a target start date or due date can be declared for each campaign.

3. Scheduling Methodology

Despite the multitude of constraints, when it comes to scheduling the solution sought is usually simple; a periodically repeating pattern of batch campaigning would be sufficient for the mainstream operations. It is therefore possible to decompose the scheduling problem in two phases: an estimation of the minimum cycle time can first be performed to determine the frequency by which a new batch can be initiated and the solution of the resource assignment problem can follow.
The minimum cycle time, Ct_{min}, is estimated using the following relation [4]:

$$Ct_{min} = max(T_i/N_i) \text{ for } i=(1,M) \quad (1)$$

where T_i is the duration of procedure i, N_i is the number of candidate equipment units for procedure i, and M is the number of procedures in the recipe. This estimate provides a lower bound on the actual minimum cycle time because it assumes disjoint equipment pools for every procedure and it ignores auxiliary

equipment and outages. When implementing the above cycle time conflicts are therefore possible and a conflict resolution scheme needs to be employed. With the emphasis placed on speed and effectiveness of the solution generation technique rather than optimality, different strategies can be devised. These strategies differ in the extent of user intervention in resolving conflicts and the length of the time window considered around a conflict. Increasing the cycle time until all conflicts across batches disappear would constitute a global change. A more local approach would be to resolve individual conflicts by exploiting all available flexibilities in scheduling the conflicting processes, preferably leaving the rest of schedule intact. Flexibilities used include the delay or interruption of an operation until needed resources become available, the reassignment of equipment or the delay of an entire batch. The user can assume zero to full responsibility about these decisions. In one extreme, the scheduling tool implements some automated logic for conflict resolution, in the other extreme all decisions are made by the user with the tool only providing feedback on possible constraint violations.

4. Example

A biopharmaceutical facility makes two different monoclonal antibody (MAB) products in two production lines that have their own bioreactor suites but share a centrifuge (S-1472) for biomass removal. The purification trains are also distinct but they share a common buffer preparation and holding area for the chromatography steps. Some buffer holding tanks are dedicated to a specific product; others can be used by both. In addition, the two production lines share two CIP skids for cleaning.

A 3.5 day cycle time is chosen for each production line. With the available main equipment this cycle time is more than sufficient to avoid any conflicts in the main equipment use. However, as it can be seen in Fig. 1, this is not the case for shared auxiliary equipment. The hollow rectangles in the Gantt chart represent periods over which a process waits for the available resources to become available before it gets executed. This waiting is possible because flexibility has been declared in the start time of some operations. More specifically, a 24hr flexible shift has been added to all CIP operations to indicate that the cleaning can delay for up to one day until the CIP skid becomes available. Similarly, the buffer preparation operations have been set to start 9 hr before they are used but with the flexibility to delay their start for up to 7 hrs. Two hours is the time needed to prepare the buffer so with the above arrangement it is certain that the buffer will be ready when needed.

Under the nominal set-up, a conflict-free schedule is possible as seen in Fig. 1. However, it is obvious that the slightest departure from this schedule (e.g. longer inoculum preparation) is bound to create new conflicts. At this point, easy rescheduling is the key. It is at the user's discretion to attempt to resolve these conflicts manually or let the tool intervene to address the problems.

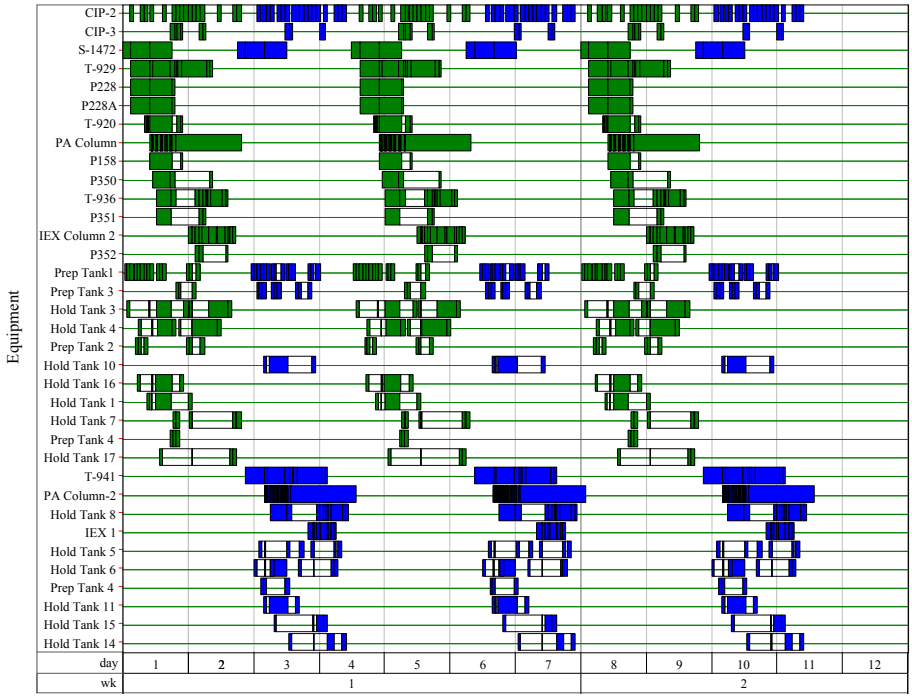

Figure 1. Equipment Gantt chart for biopharmaceutical example process

5. Conclusions

In biopharmaceutical processing tight constraints, especially in auxiliary equipment and resources, dictate the schedule. A rich representation of all recipe and facility constraints is needed so that all possible conflicts can be identified. The key to resolving conflicts is to know where to add and exploit flexibility. Involving the user in the decision process ensures that the generated solutions are realistic and acceptable albeit not necessarily optimal.

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