A MULTI-OBJECTIVE APPROACH ON THE OPTIMAL PRODUCTION AND MAINTENANCE PLANNING OF BIOPHARMACEUTICAL PROCESSES UNDER PERFORMANCE DECAY USING A CONTINUOUS-TIME FORMULATION

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Abstract

This paper presents a multi-objective approach considering a mixed integer linear programing (MILP) model, based on a continuous-time Resource Task Network (RTN) formulation, for the optimal planning management of biopharmaceutical processes. The model assesses the manufacturing constraints for the determination of the optimal production schedule while considering the simultaneous maintenance planning of downstream units, subject to performance decay. The optimal results of an illustrative medium-term planning problem of a biopharmaceutical process, addressing the main bioprocesses regulations, is analysed through a multi-objective approach considering the augmented ε-constraint method. The evaluation of the Pareto sets for two bi-objective analyses is performed, considering the profit maximisation with the minimisation of the number of intermediate maintenance operations and the maximisation of average service level, while comparing the different solutions towards the decision maker's strategic and operational goals.

Keywords

Multi-objective optimisation, production and maintenance planning, performance decay.

Introduction

The management of current multipurpose plants has challenged the development of efficient tools for production planning/scheduling optimisation. Harjunkoski et al. (2014) recently reviewed several industrial applications of mathematical models and methods successfully implemented. Despite the increasing interest of industry stakeholders to understand the potential of these tools to optimise their operations, a major challenge arises to overcome the wide diversity of operational problems. For example, the process modelling often stumbles either to detail specific operational requirements or to tackle large temporal horizons due to inherent computational limitations. Therefore, the research community has been exploring improved model formulations to address real industrial management problems, aiming the implementation of optimal decision-making production systems.

The case of the pharmaceutical industry, due to its process network complexity, has been the drive for several studies of optimisation models and techniques (Moniz et al., 2014). More recently, the increasing relevance of novel bioprocesses have defined new modelling challenges, either addressing the strict process regulatory policies on products storage shelf-life and biological variability or the process equipment compliance to product quality. These biopharmaceutical drugs are complex medicinal

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biomolecules with pharmacological activity used for therapeutic or in vivo diagnostic purposes. The manufacturing process generically defines an upstream suite that include all tasks associated with cell culture and maintenance of the active biological ingredient, and a downstream suite comprise the chemical/physical operations in the isolation and purification of the drug. The ability to genetically manipulate highly effective biotherapies such as vaccines, cell or gene therapies, therapeutic proteins hormones, monoclonal antibodies, cytokines and tissue growth factors, is promoting a steady growth in the pharmaceutical market.

The wide research on planning and scheduling models in the pharmaceutical industry spreads from the management of drug portfolio pipelines to the design optimisation of highly specific steps of the manufacturing process. But only recently these biotechnological processes have been gathering more attention due to its biological specificities, so it is noticed a relatively small number of research papers covering planning and scheduling problems of biochemical processes. Noteworthy, the work by Lakhdar et al. (2005) firstly proposed a discrete-time MILP model for the optimal production and cost effective sequence of manufacturing tasks for a medium-term horizon, underlining the advantages of planning optimisation. More recently, Kabra et al. (2013) and Vieira et al. (2016a) developed a continuous-time model for multi-product campaign scheduling of biopharmaceutical processes based on State Task Network (STN)/ Resource Task Network (RTN) framework, while Siganporia et al. (2011) developed a discrete-time model with a rolling time horizon for the capacity planning across multiple biopharmaceutical facilities, are some examples.

Optimisation models have been further extended to approach different critical operational aspects of the production planning process. One is related to the planning of maintenance operations, aiming to provide an integrated solution defining which maintenance activities occurs (and when) to restore an item to a given condition, such that one or several objectives are optimised. As example, the simultaneous production and maintenance planning under a performance decay applied to biopharmaceutical processes problems was only recently proposed by Liu et al. (2014). In that work, the planning of a biopharmaceutical process is proposed with the development of a discrete-time model based in Lakhdar et al. (2005), optimising the number of maintenance operations considering the yield decay of resins in downstream purification with the number of batches produced. The premise relies on the fact that chromatography is one of the most common techniques for purification and separation in the biopharmaceutical industry. Chromatography resins have a limited lifetime and, due to their high cost, the decision when to perform maintenance operations is of key importance in the purification performance. Therefore, it is possible to optimise the production schedule on whether to continue using the resin with a lower yield or to perform the regeneration to its initial level, subject to a maintenance cost.

The study discussed in this paper follows the same maintenance propositions by Liu et al. (2014), with the determination of the optimal production schedule while addressing the main specific requirements of biopharmaceutical processes. It extends the previous work by Vieira et al. (2016b), that discussed the results advantage of a continuous-time model approach when compared to a discrete-time formulation. In this work, regarding the multiple strategic and operational constraints of these bioprocesses, we will formulate a multi-objective approach to these planning problems, evaluating the solution quality provided to the decision maker and its relevance to take the best solution towards the management optimisation of the industrial process.

Problem Statement

In this work, we highlight the study of a multi-objective approach to determine the optimal production schedule of a biopharmaceutical process with integrated maintenance operations due to performance decay. The biopharmaceutical manufacturing is commonly refereed as a two stages process: all products undergo upstream cell-fermentation to produce intermediate products and then downstream purification processing to obtain the final product. The production facilities typically operate on a campaign basis, to avoid long changeover times and cross-product contamination, and are exploring continuous operation modes due to enhanced ability to control process parameters. Although each stage may take place on multiple sequential suites, the fact that the processing times in these bioprocesses are rather long, it is reasonable to assume an aggregate production task per each process stage: a single fermentation step with an average production titre and a single chromatography step with a known characteristic decaying yield of the resin versus the number of cycles. The maintenance operations are therefore to be scheduled on the downstream processing units to perform the replacement of the chromatography resin.

The strategic and operational objectives for a biopharmaceutical manufacturer are directly linked to the different stakeholders and operational restrictions. Even though the long-term goal of any business relies in the maximization of its shareholder value, the process objectives can include the minimization of operational costs, the maximization of profit or service level, among others. As previously discussed by Vieira et al. (2016), the main manufacturing constraints of these bioprocesses assess batch and/or continuous process steps, multiple intermediate deliveries with backlog penalties, sequence dependent changeover/setup operations, shelf-life limitations of stored intermediates/products, and the track-control of the production lots for regulatory policies. And further, the simultaneous optimisation of the required maintenance plan with the campaign schedule increases the competition among operational factors.

Most optimisation models rely in providing a solution accounting a single objective function. However, the best decision for the optimal company management can often imply the simultaneous evaluation of different goals, increasing the interest for multi-objective approaches. For that reason, in this study we will first consider a common single objective problem where the operating profits are maximised, followed by two multi-objective problem comparing the profit results against the number of maintenance operations required and the demand service level. On the former, the costs of the high-performance purification steps are usually difficult to quantify, whereas the replacement of a resin before the end of its lifetime can often imply an investment loss not quantified in the profit. On the later, the late deliveries must be minimised by ensuring an adequate supply of product, but foremost to keep a high client satisfaction, which could be lost with a single maximization of revenues.

Applied to an industrial-based planning problem, the goal is to determine a solution with an optimal task-unit assignment and sequencing, sequence dependent changeover/set-up, the temporary storage allocation, produced campaign lots, sales/late deliveries and maintenance tasks schedule of the downstream units, given:

(i) the product recipes in terms of their respective RTN framework;

(ii) the time horizon, product demands and due dates;

(iii) the characteristics of the processing/storage units and sequence-dependent changeover/setup times;

(iv) processing rates and the task-unit suitability;

(v) the shelf-life storage of intermediaries/products;

(vi) the manufacturing, changeover and storage costs for all materials, the value of the products, and late delivery penalties;

(vii) the duration and cost of maintenance operation, with information of the decaying yield with the number of batches produced.

So as to maximize the production profit (single objective problem) and implement two multi-objective assessments by (i) minimising the number of maintenance operations and (ii) maximising the service level.

Mathematical Formulation

The problem defined above is formulated through a MILP continuous-time model based on the RTN framework, addressing the identified constraints of biopharmaceutical processes. The RTN process framework unifies the problem formulation in terms of two sets of entities: tasks and resources, where a task i is any operation that transform any set of resource r (materials or processing units) (Pantelides, 1994). The base formulation is detailed in Vieira et al. (2016), considering a continuous-time representation with single time-grid common to all equipment resources. This approach divides the planning horizon into a number of time slots with unknown duration (to be optimised) given by a number of time events t. Since in a continuous-time formulation it is unknown a priori how many slots are required to find the global optimal solution, a standard iterative procedure is used, where one keeps incrementing the number of events/slots and solving the optimisation problem as long as improvements in the objective function are observed (Mendez et al., 2006). Only one processing task can occur per time interval and it could comprise the allocated time for the sequence dependent changeover/setup and/or maintenance. Despite the original formulation by Vieira et al. (2016a) allows some tasks to span across a number of time slots, in these approach, for simplification, it is assumed that all tasks can last only one time slot $[t,t+1]$, which allows to consider a single time index t in the main decision variables. This formulation is later extended to address the maintenance planning optimisation based on the work by Liu et al. (2014).

As a short overview of the model, the main decision variables, given a set of events t, are: $N_{i,l,t}$ (binary) is active if lot l of task i (batch or continuous) starts at event t, and $\xi_{i,l,t}$ (integer) gives the amount of material processed on time slot $[t,t+1]$. The excess balance of each resource r is determined in each event point (with absolute time T_t) by the variable $R_{r,l,t}$. These variables include an additional lot index l to comply with production regulations, allowing the blending/splitting traceability by labelling each campaign lot. The maintenance formulation is based on the tracking of the number of batches produced per unit, indexing the sequential nth batch since the last maintenance and, accordingly, link each batch to the respective resin yield decaying profile. The binary variable $M_{r,t}$ indicates whether the maintenance is performed in the equipment unit E at the beginning of time event t, taking into account the respective performance decay (production yield versus number of batches produced since last maintenance).

Regarding the multi-objective approach, the formulation would not provide a single solution that optimises both objectives under analysis, but instead allowing the decision maker to search for a compromise among a range of solutions. According to Mavrotas (2009), the multi-objective methods can be classified as a priori, interactive and a posteriori (or generation), based on the phase in which the decision maker is required to express his/her preference: in a priori method the decision maker should set a goal or weights to the objective function before the solution process; in an iterative method he/she drives a iteration search of successive calculations until convergence; and in a posteriori method the decision maker is able to evaluate a representation of all efficient solutions generated. Acknowledging the limitations of the former methods, this later method provides significant advantages generating a Pareto set of solutions which upturns the confidence of the decision maker, but is highly demanding in computational effort. Among the existing literature methods, our proposed model approach implemented the augmented ε-constraint method (AUGMECON) developed by the same author and applied as follows: the first step consists in the lexicographic optimisation of the payoff table, to determine the range of each one of the objective functions that are used as constraints; then each range is

divided into equal intervals, defining the grid points that are used to calculate the parametric solutions; and with the total number of runs is possible to generate the Pareto set. The density of the set representation can be defined with a higher number of grid points but a trade-off should be evaluated with the cost of higher computational time.

Finally, the objective functions for the proposed MILP model approach for the planning problem optimisation: Eq. (1) consider the profit maximisation with final products sales (υ_r^s) by penalising the costs of manufacturing (c_i^{mf}), storage allocations (c_r^{st}), changeovers/setup ($c_{i,i'}^{ch}$), extended shelf-life wasted amounts (c_r^d), late backlogs (c_r^u) and maintenance operations (c_r^m); Eq. (2) the number of intermediate maintenance operations; and Eq. (3) the average service level per total demand, accounting for the backlogs throughout the planning horizon.

$$profit = \sum_{r\in P}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}} \upsilon_r^s(-\Pi_{r,l,t}) - \sum_{i\in I}\sum_{l\in L_i}\sum_{\substack{t\in T\\ t\neq|T|}} c_i^{mf}\xi_{i,l,t} - \sum_{r\in M_{st}}\sum_{l\in L_r}\sum_{t\in T} c_r^{st}R_{r,l,t} - \sum_{i\in I}\sum_{i'\in I}\sum_{\substack{t\in T\\ t>1}} c_{i,i'}^{ch}C_{i,i',t} - \sum_{r\in M/RM}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}} c_r^d W_{r,l,t} - \sum_{r\in P}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}} c_r^u\Pi_{r,l,t}^u - \sum_{r\in E}\sum_{\substack{t\in T\\ t\neq|T|}} c_r^m M_{r,t} \quad (1)$$

$$maintenance\ op = \sum_{r\in E}\sum_{\substack{t\in T\\ t\neq|T|}} M_{r,t} \quad (2)$$

$$service\ level = 1 - \sum_{r\in P}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}} \Pi_{r,l,t}^u / demand \quad (3)$$

Illustrative example

The example reproduces the medium-term planning problem suggested by Lakhdar et al. (2005) based on a real industrial case: a two-stages process in a continuous production mode, with two upstream fermentation suites [J1 & J2] and two downstream purification suites [J3 & J4] per stage (Figure 1). The problem considers a demand profile of 34 batches of three products (12 of P1, 6 of P2 and 16 of P3) to be delivered in five due dates *d* for a 360 days horizon. One batch should be considered as a quantity unit, undisclosed for confidentiality reasons. Maintenance and performance decay data was taken from Liu et al. (2014). For this approach, the variable assessing the extent of tasks is set as continuous with an upper limit of 180 days and the costs of the first setup and maintenance operations were disregarded. The model was implemented in GAMS (GAMS 24.5.6 WIN VS8 x86) and solved with CPLEX running on an Intel Xeon X5680 64-bit at 3.33 GHz with 24 GB of RAM.

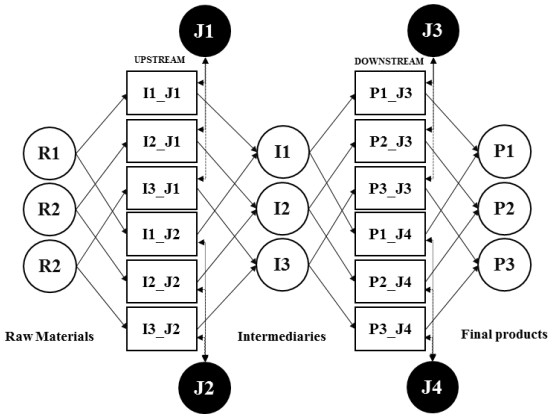

Figure 1. RTN production facility layout for illustrative example.

Single objective approach

Considering the single objective of the profit maximisation, the iterative procedure reached the global optimal schedule solution with 7 event points (including the initial point *T*=0 days) for a profit of 440,7 real monetary units (rmu), since an increase in the number of event points does not verify the improvement of the profit solution. The GAMS results statistics are summarized in Table 1 and the Gantt chart is presented in Figure 2.

The schedule provides the optimal solution for the sequencing and allocation of the different production tasks in each processing suites, with identification of the campaign lot-number and size/duration for each intermediate/product (in brackets, with the outputs of final product accounting the yield decay). There is a total unfulfilled demand of 0.15 batch (0.05 of P1 and 0.1 P3), and extra late deliveries of 0.3 batch verified for $P1^{L3}$ at event t_6. Results show four intermediate maintenance operations - [M] mark - in the downstream resin and seven storage allocations - [S] mark - for a total amount of 0.2 batch of $I3^{L3}$ and 17.3 batches of final products. Along with the initial equipment setup, 7 intermediate sequence-dependent changeover/set-up operations are scheduled, which our formulation allows to occur at the beginning or end of the interval for the upstream units, granting more time available for the production task. The results show the planning flexibility provided by the continuous time-grid, with different length intervals to accommodate the suitable production demand and respective support operations.

Table 1. Optimal GAMS results statistics

Events	Equations	Total variables	CPU (s)	Profit (rmu)
6	6728	3876	78	425.8
7*	8714	4709	317	440.7
8	10910	5584	831	440.7

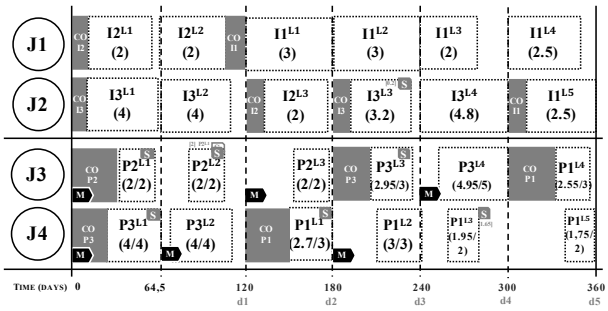

Figure 2. Optimal production and maintenance schedule of example for a profit of 440.7 rmu (in brackets, the outputs of final product accounting the downstream yield decay).

Multi-objective approach

In the multi-objective approach, acknowledging that the global optimal solution was obtained with 7 event points, the analysis of the Pareto sets is performed for the two bi-objective cases: (A) maximising the profit vs minimising the number of intermediate maintenance operations (Figure 3), and (B) maximising the profit vs maximising the service level (Figure 4).

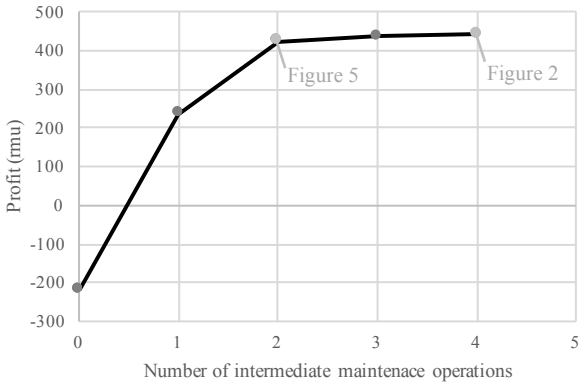

Figure 3. Pareto set for the profit maximisations vs the number of intermediate maintenance operations minimisation for example (A).

(A) Since the problem statement disregards the time dedicated to the maintenance operations, as well as the high investment regarding the replacement of these downstream chromatography columns, the decision maker can prefer an alternative schedule solution where the utilization of installed resins is increased. The Pareto set displayed in Figure 3 shows that with two less intermediate maintenance operation, the schedule solution of Figure 5 generates a profit of 422.7 rmu, which corresponds to a difference of less than 4% to Figure 2 solution. Although increasing the costs of late deliveries, this solution increases the utilisation of each resin capacity before its ensuing maintenance, which for this case was set as maximum of 11 batches corresponding to a minimum yield of 65%.

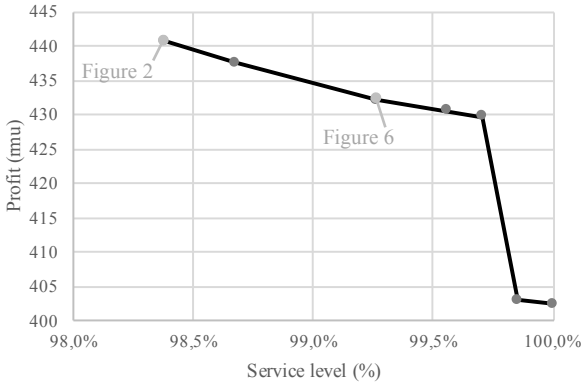

Figure 4. Pareto set for the profit maximisations vs the service level maximisation for example (B).

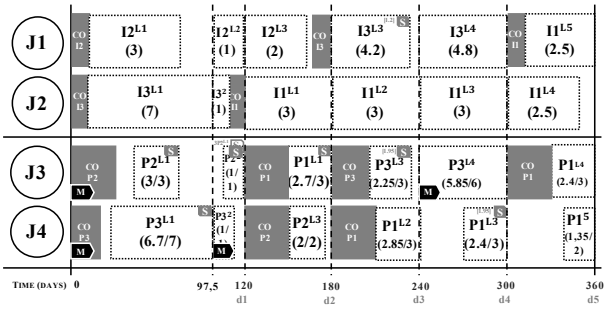

Figure 5. Optimal production and maintenance schedule with two intermediate maintenance operations (profit 422.7 rmu).

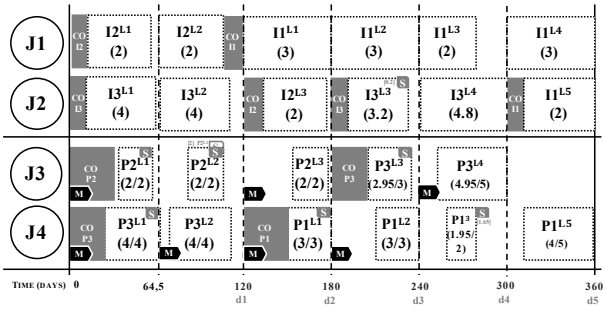

Figure 6. Optimal production and maintenance schedule for an average service level of 99.3% (profit 432.1 rmu).

(B) Accounting for the service level and customer satisfaction, which is penalised by the backlogs of late deliveries along the horizon time events, the decision maker can consider that 98.4% is a low proposition for the company standards, as verified

in the Pareto set of Figure 4, defining as company policy that it could never be lower than 99%. For that reason, a schedule solution for a service level of 99.3% (profit 432.1 rmu) is generated in Figure 6, requiring as additional 4th intermediate maintenance operational on unit J4 at the third event slot to be able to satisfy the entire demand of 6 batches of P1 at the due date *d3* (240 days). The increase in the service level is mainly accomplished by adding extra maintenance operations, reducing the impact of the production output decay but incurring in extras maintenance costs that lowers the profit solution.

These multi-objective analyses enable the decision maker to have a broader look to the range of possible planning solutions, in particular to weight the different strategic policies and guidelines targeted for the company operation. Its relevance clearly stands to support the best optimal planning solution while dealing with conflicting objectives instead of a single profit maximisation.

Conclusions

In this work, a MILP/RTN continuous-time single grid formulation was applied to an illustrative medium-term planning problem, successfully addressing the specific constraints of biopharmaceutical production subject to performance decay. The formulation results discuss the importance of an integrated maintenance planning and its impact in the production optimisation, highlighting the advantages of a continuous-time single time-grid horizon to determine the optimal plan. A multi-objective optimisation approach is also implemented, considering the augmented ε-constraint method, providing an enhance decision support towards company's strategic objectives for the optimal process management. Future work will explore the advantages of different multi-objective assessments and the challenges of the implementation of the optimisation model as a decision support tool, assessing the requirements of the decision maker to solve these industrial planning problems and its suitability to real production environments.

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