Optimal planning and campaign scheduling of biopharmaceutical processes using a continuous-time formulation

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ABSTRACT

This work addresses the optimal planning and campaign scheduling of biopharmaceutical manufacturing processes, considering multiple operational characteristics, such as the campaign schedule of batch and/or continuous process steps, multiple intermediate deliveries, sequence dependent changeovers operations, product storage restricted to shelf-life limitations, and the track-control of the production/campaign lots due to regulatory policies. A new mixed integer linear programing (MILP) model, based on a Resource Task Network (RTN) continuous time single-grid formulation, is developed to comprise the integration of all these features. The performance of the model features is discussed with the resolution of a set of industrial problems with different data sets and process layouts, demonstrating the wide application of the proposed formulation. It is also performed a comparison with a related literature model, showing the advantages of the continuous-time approach and the generality of our model for the optimal production management of biopharmaceutical processes.

Keywords: biopharmaceutical plants, planning and campaign scheduling, optimisation, Mixed Integer Linear Programming

1 INTRODUCTION

The competitiveness in current globalised markets request industrial companies to manage more efficiently the available manufacturing resources, so as to ensure high levels of responsiveness under high production variability. The case of the pharmaceutical industry is a good example on how market is driving the change on product development and manufacturing. This sector is exploring the development of highly effective bioengineered drugs for the treatment of diseases such as cancer, autoimmune disorders, organ transplant rejection, and many other new drugs are in clinical trials. With the number of biologic drugs increasing, manufacturers are being prompted to find flexible, cost-efficient and environmentally feasible solutions for global scales of production. To tackle these challenges, the adoption of decision-support tools have been outspreaded from the management of the research and development (R&D) drug portfolio to the optimal design/operation of biopharmaceutical facilities (Ramasamy et al., 2014).

In what concerns the operations management, planning and scheduling decision-making has become an essential issue to the majority process industries. The increasing complexity in managing batch/continuous processes caught the interest of the research

community to develop efficient modelling approaches to promote operational performance. Several industrial applications of scheduling models have been quite successfully implemented, as stated by Harjunkoski et al. (2014) and Moniz et al. (2014b). Still, despite the major research developments reported in the literature, the implementation of such models to solve real industrial problems often stumbles, in either modelling specific operational requirements or tackling large planning horizons, constrained by the inherent computational complexity. The development of optimisation tools capable to solve real large-scale industrial problems remains a challenge and new formulations for modelling complex process constraints are required, aiming the integration with common decision-making systems. In the particular case of the biopharmaceutical industry, the development of models for production planning and scheduling of biopharmaceutical processes is acknowledged that has been fairly unexplored.

In this paper, we tackle this important problem and propose the development of a campaign planning/scheduling model addressing several operational constraints of the biopharmaceutical processes, such as: a) batch and continuous tasks; b) multiple intermediate deliveries, c) sequence-dependent changeovers; d) product shelf-life limitations; e) regulatory track-control of the production/campaign lots. To the best of our knowledge, very little work has addressed the bioprocessing context, notwithstanding the application of some of these operational features to other planning and scheduling problems. A mathematical formulation is proposed to model these operational requirements and two literature-based industrial problems are solved. A results comparison is performed with a literature model considering different time modelling approaches (discrete versus continuous-time), highlighting the performance advantages of the proposed formulation. The remainder of the paper is structured as follows: the next section presents the background in biopharmaceutical planning/scheduling optimisation; section 3 introduces the problem definition and presents the mathematical model formulation; in section 4, two problems are presented and discussed regarding its numerical results; finally, section 5 summarises the main conclusions and future work.

2 BACKGROUND

2.1 (Bio)Pharmaceutical planning/scheduling optimisation

Biopharmaceutical drugs refer to complex medicinal biomolecules with pharmacological activity used for therapeutic or *in vivo* diagnostic purposes. The ability to genetically manipulate (by recombinant DNA or hybridoma technology) highly effective biotherapies such as vaccines, cell or gene therapies, therapeutic proteins hormones, monoclonal antibodies, cytokines and tissue growth factors, has represented a breakthrough in the pharmaceutical industry. The biotech sector has been increasing steadily with a strong pipeline of drugs under clinical trial, representing in 2010 more than $100 billion in sales worldwide with over than 200 biologics on the market (Walsh, 2010, Mehta, 2008).

Since the introduction of recombinant human insulin in the 1980s, these molecules are produced by means of genetically engineered biological organisms other than direct extraction from native sources. The manufacturing process is generically composed by two steps: the upstream processes include all tasks associated with cell culture and maintenance of the active biological ingredient, and the downstream processes comprise the chemical/physical operations in the isolation and purification of the drug. The

primary fermentation stage consists in the inoculation of the target drug from a cell bank in a growth medium, harvested when reached the optimal concentration. The following purification procedures typically consider filtration of the source material (suitable for blending product variants), followed by chromatography to select the target proteins. The product is then bulked and stabilised with binding agents according to specifications, from where it is lyophilised to remove water and other solvents. This final product can be stored, packaged and distributed to retail or directly to consumers. In each process stage, product quality control tasks are required to assure process licensure by regulatory agencies. The same regulatory control is extended to the entire process components, where any change in plant, equipment or process specifications must be certified for each region of the world where the product is being sold (Leachman et al., 2014).

Most of these manufacturing processes are relatively new and require continuous improvement due to their long lead times, where the main challenge relies in the large scale production of these biomolecules with a stable output quality. For that reason, the mechanisms to produce, purify and preserve the drug have also been subject to research development, along with the therapeutic discoveries. The provision of sufficient output capacity to meet an expected demand, within the patent protection lifespan and without disregarding all the stringent regulations, resumes the production challenge.

The development of planning and scheduling tools are essential in industrial environments to maximise production efficiency and resources assignment. Bioprocess automation has been enhancing the control and monitoring of manufacturing parameters, as reviewed by Junker and Wang (2006), with relevant achievements in applications of process analytical technology (PAT) for quality and performance attributes. But besides the manufacturing optimisation, the operations planning ranges from the portfolio management of biopharmaceutical drugs development to the design optimisation models for specific steps of the production process. It is acknowledged that the extended drug development process and the high uncertainty of the drug's clinical success commonly leads to a pipeline of compounds under trial. As example, Rajapakse et al. (2005) developed a prototype decision-making application based on simulation tools, to assist the management of the R&D portfolio by accessing both the therapeutic drug development activities and its resources flows, and Farid et al. (2007), Farid et al. (2005) presented the *SIMBIOPHARMA* software tool, able to evaluate manufacturing strategies of drug candidates in terms of cost, time, yield, resource utilisation and risk uncertainty. Whereas addressing some specific aspects of process design, Brunet et al. (2012) addressed the design of upstream/downstream units in a single-product processes with a mixed integer dynamic optimisation and Liu et al. (2015) have proposed significant research work on the optimisation of downstream chromatography sequencing and column sizing strategies. However, it is noticed a relatively small number of research papers addressing the production planning/scheduling of biochemical processes, either encompassing the process performance optimisation as well as operating costs, resource utilisation or uncertainties (Vieira et al., 2015). Lakhdar et al. (2005) proposed a discrete time MILP model for the optimal production and cost effective planning of manufacturing tasks for a medium term horizon of 1-2 year year and compared with an industrial rule-based approach. Then, Lakhdar et al. (2007) addressed a multi-objective long term planning horizon and Lakhdar and Papageorgiou (2008) considered the uncertainty in operational parameters, e.g. fermentation titres. More recently, Kabra et al. (2013) developed a continuous-time multi-period scheduling of a multi-stage multi-product process based on State Task Network framework, Liu et al. (2014) extended a production optimisation model to include maintenance planning while considering the performance decay of the

chromatography resins, Siganporia et al. (2014) developed a discrete-time model with a rolling time horizon for the capacity planning across multiple biopharmaceutical facilities, and Shaik et al. (2014) proposed two model formulations based on discrete and continuous-time representations for the scheduling operation of biotech batch plants.

Despite the increasing interest within the topics of biopharma, the development of modelling solutions for planning and scheduling problems remains a challenge, as well as exploring the wide intricacy of the operational aspects of these processes. The complexity of planning/scheduling problems in the pharmaceutical sector have been subject to significant attention towards the use of optimisation models and techniques (Shah, 2004). The novelty of these bioprocesses have placed new challenges in modelling research, either addressing the strict process regulatory constraints, products storage shelf-life limitations and biological variability, or campaign basis to comply with product quality requirements and minimise cross-product contamination. Simaria et al. (2012) identified that biopharmaceutical facilities will tend to adopt a smaller scale with multiple bioreactors, able to reduce the capital cost and optimising the number of production batches to match uncertain demand. Traditional batch processing may still remain the predominant approach to manufacturing (Ramasamy et al., 2014), but technological enhancements in continuous processes (e.g. perfusion technique) are showing improved productivities and operational outcomes. Likewise, to comply with process licensure, the option to use typical stainless steel vessels, with required cleaning in-between batches, can be evaluated against the alternative of single-use disposable equipment.

Noteworthy, the general problem of planning and scheduling operations has been gathering extensive research in process industry, with relevance to modelling and optimisation scheduling methodologies as reviewed by Mendez et al. (2006) and Harjunkoski et al. (2014). The approaches based on a unified process representation, both the State-Task Network (STN) and the Resource-Task Network (RTN) proposed by Kondili et al. (1993) and Pantelides (1994) respectively, have proven to be effective in most classes of scheduling problems. As an example of a real pharmaceutical industrial scheduling problem, Moniz et al. (2013) proposed an MILP discrete time formulation based on the RTN framework, considering some production constraints, such as sequence-dependent changeovers, temporary storage in processing units, lots blending/splitting and materials traceability.

The boundaries of planning/scheduling problems are typically associated with the type of decision detail required for a given time-horizon, ranging from several hours/days (short-term scheduling) to several weeks/months (campaign scheduling/mid-term planning). Regarding the time-horizon model representation, two different approaches have been explored: discrete-time and continuous-time. The discrete-time formulations considers the division of the time horizon into equal length intervals, assuming fixed processing times multiple of those intervals, see for instance the recent work by Moniz et al. (2014a), while the continuous-time formulations can be more sensitive to changes in the tasks duration, for example to deal with continuous processes, where the start/duration of the scheduled slots in the time horizon remains a variable. The continuous-time formulations can rely on a single time-grid common to all resources (Maravelias and Grossmann (2003) and Castro (2010)) or multiple time-grids for each resource of the process (Shaik and Floudas (2008) and Shaik and Floudas (2009)). However, it is acknowledged that each model approach is strongly determined by the selected problem representation of the material flow and unit specific constraints, which impacts on its complexity and performance.

Considering the characteristics of the planning and campaign scheduling problems in a biopharmaceutical facility, the proposed MILP model is based on the RTN framework using a continuous-time formulation with a single time-grid. The mathematical formulation aims at addressing the main planning/scheduling constrains of these bioprocesses, namely, the schedule of batch and/or continuous process steps, multiple intermediate deliveries, sequence dependent cleaning operations, storage of products regarding shelf-life limitations, and the track-control of the production lots for regulatory policies.

3 MODEL CHARACTERISTICS

3.1 Problem definition

This study proposes the development of a continuous-time MILP model, based on the RTN framework, to address the optimal planning of the production and determine for each campaign the schedule with unit–task allocations, the task timings and the flow/store of material through the plant of a biopharmaceutical process. The objective is to maximise the profit by determining the optimal task-unit assignment and sequencing, sequence dependent changeovers, the temporary storage allocation, campaign-lots number and duration/size and eventual blending/splitting requirements, given:

(i) the product recipes in terms of their respective RTN framework;
(ii) the product demands and due dates;
(iii) the characteristics of the processing units;
(iv) processing times, operational costs and the task-unit suitability;
(v) the shelf-life storage of intermediaries/products;
(vi) the value of the products;
(vii) and the costs for all materials.

3.2 Mathematical Formulation

The problem defined above is modelled through a RTN continuous-time formulation based on the model proposed by Castro et al. (2004), which accesses our premise to address both batch and continuous processes. It must be noted that, by process definition, in a batch operation mode the materials are entirely consumed at the start of the respective production task, and the amount produced is made available only at its finish. However, in a continuous operation, a production flow rate is verified along the duration of the task, which allows that sequential continuous tasks can occur simultaneously. The identified features of planning and campaign scheduling problems in biopharmaceutical processes are addressed by extending the baseline formulation with a new set of variables and constraints detailed as follows. The mathematical nomenclature can be found at the end of this article.

3.2.1 Resource Task Network framework

The RTN process framework unifies the model formulation in terms of two sets of entities: tasks and resources. A task is an operation that transforms a set of resources, which includes all entities involved in the process such as materials or processing units. The tasks can interact with resources discretely at its start and finish (batch tasks), and/or continuously at a rate that remains constant throughout its duration (continuous tasks). The initial formulation proposed by Pantelides (1994) considered a discrete-time formulation, dividing the time horizon H into fixed and uniform time intervals. Instead, in a continuous-time

formulation the length of each interval is unknown, being more sensitive to small changes in task durations (Schilling and Pantelides, 1996). The continuous-time formulation presented in this paper considers a common time grid to all resources and events taking place in the planning horizon. As shown in Figure 1, the time horizon *H* is divided into a given number of slots (*T*-1), but contrary to its discrete-time formulation, the absolute time of the event point t is determined through variable T_t.

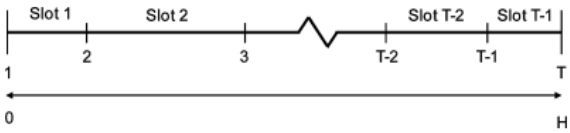

Figure 1 – Single time grid for the continuous-time model

The RTN continuous-time formulation, as well as its discrete-time counterpart, considers binary *N* and continuous ξ variables to characterise the event of task *i* starting at point t and ending at (or before) point $t'>t$ (Castro et al., 2004). Moreover, to assure typical regulatory policies of the pharmaceutical processes (Moniz et al., 2013), these variables are now extended to include a lot index *l*, congregate 4-indeces $iltt'$. The binary variable $N_{iltt'}$ is equal to one if lot *l* of task *i* starts at event point t and finish until event point t', $\xi_{i,l,t,t'}$ gives the lot amount of material processed within the same time slot $[t,t']$. This modelling feature enhances the ability to trace the schedule of different lots of the same product campaign that, for example, could be blended/splitted during the process. The extent variable of the task for a certain time interval defines the total campaign-lot amount to be produced, suitable to address the size/duration of the campaign according to the requirements of the production plan.

The biopharmaceutical processes can consider either batch and/or continuous tasks throughout its production steps, according to the selection of technological equipment. The amount of each resource produced or consumed is assumed to be proportional to the characteristic variables of the task by a set of structural parameters. The parameters $\mu_{i,r}^{p}$ and $\mu_{i,r}^{c}$ associate the discrete interactions with the $N_{i,l,t,t'}$ variables, used whenever the amount of resource r produced or consumed is independent of the amount processed, as it is the case of equipment items. For material resources, discrete iterations parameters $v_{i,r}^{p}$ and $v_{i,r}^{c}$ links the extent variables $\xi_{i,l,t,t'}$ to the amount processed. A task can also interact in a continuous manner with one or more resources for its duration (typically material resources), where parameter $\lambda_{i,r}$ accounts for the rate of generation of the resource associated with the extent variable $\xi_{i,l,t,t'}$. As example, Figure 2 shows a general RTN representation for a process composed by two consecutive tasks. The batch task (TB) consumes material A and produces material B, while the continuous task (TC) consumes material B and produces material C. Moreover, task TB requires the processing unit U and task TC the processing unit M. The dashed lines represent discrete interactions, while solid lines depict continuous interactions (noted that interactions with equipment are, by model definition, always discrete). In each connection the previous parameters are identified, where, for each task, negative values will grant the consumption of the respective resource r on task *i* for one interval $[t, t']$, whereas positive values denote production.

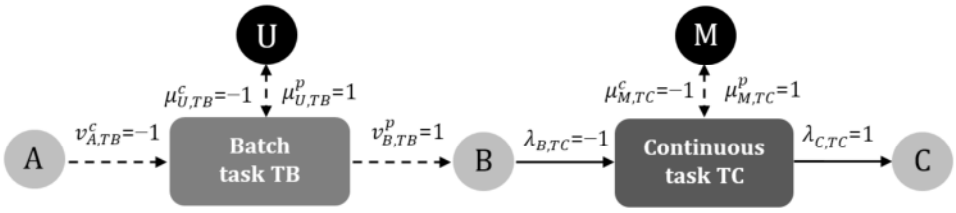

Figure 2 – RTN process representation

3.2.2 Timing constraints

To account for the duration of a task *i*, it is assumed that the processing time can be given by a constant α_i plus a term proportional β_i to the amount of material being processed, as $(\alpha_i + \beta_i \xi_{i,l,t,t'})$. This allows to represent all types of tasks, for example, either a batch task I_b with a fixed duration (e.g. α_i>0 and $\beta_i = 0$) or a continuous task I_c with processing rate ρ_i (e.g. α_i=0 and β_i=1/ρ_i) with $\rho_i \in [\rho_i^{min}, \rho_i^{max}]$. With the assumption that only one task per lot can be executed at any processing equipment ($r \in E \backslash E_{st}$) at each time interval, equation 1 imposes that the difference between the absolute times of two event points $[t, t'] > 0$ must be either greater or equal than the processing time of the tasks starting and finishing within the interval. Thereby, the first term is referred to the sum of batch tasks and the second to continuous tasks. Since this formulation allows the relaxation of the duration of the tasks in each time interval, equation 2 assures that, if required, time constraints are satisfied for batch tasks subject to zero-wait policies (I_{zw}) or for continuous tasks that must exceed a certain minimum rate (I_{mr}).

$$T_{t'} - T_t \geq \sum_{i \in I_b} \sum_{l \in L_i} \mu^p_{i,r} \left(\alpha_i N_{i,l,t,t'} + \beta_i \xi_{i,l,t,t'}\right) + \sum_{i \in I_c} \sum_{l \in L_i} \left(\frac{\mu^p_{ir} \xi_{i,l,t,t'}}{\rho_i^{max}}\right) \quad (1)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t', t \neq |T|$$

$$T_{t'} - T_t \leq H \left(1 - \sum_{i \in I_{zw}} \sum_{l \in L_i} \mu^p_{i,r} N_{i,l,t,t'} - \sum_{i \in I_{mr}} \sum_{l \in L_i} \mu^p_{i,r} N_{i,l,t,t'}\right) + \sum_{i \in I_{zw}} \sum_{l \in L_i} \mu^p_{i,r} \left(\alpha_i N_{i,l,t,t'} + \beta_i \xi_{i,l,t,t'}\right) + \sum_{i \in I_{mr}} \sum_{l \in L_i} \left(\frac{\mu^p_{i,r} \xi_{i,l,t,t'}}{\rho_i^{min}}\right) \quad (2)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t', t \neq |T|$$

To withhold the combinatorial extent of variables and constraints, it is reasonable to introduce in the formulation a parameter $\Delta t = (t' - t)$ to define the maximum number of consecutive events points allowed for each task to occur. The use of a fixed value for Δt is quite reasonable in cases where it is expected that few event points exist between the beginning and end of a task, but this parameter should be evaluated for each problem to not compromise the model feasibility or reach suboptimal solutions. To simplify the model formulation, we will consider a single

Δt parameter only applied to batch tasks, assuming, without loss of generality, that any instance of tasks performed in a continuous mode can last for only one time interval ($\Delta t = 1$). Since in each time interval only one task can take place in each equipment resource, the previous general time equations 1 and 2 can be rewritten to consider this Δt approach for either batch tasks (equations 3 and 4) and continuous tasks (equations 5 and 6). Moreover, each equation considers the additional time related to task changeover procedures ($\delta_{i,i'}$), to occur within the time interval when changeover/set-up is required to take place in the corresponding unit ($C_{i,i',t'} = 1$).

$$T_{t'} - T_t \geq \sum_{i \in I_b} \mu_{ir}^{p} \left(\sum_{l \in L_i} (\alpha_i N_{i,l,t,t'} + \beta_i \xi_{i,l,t,t'}) + \sum_{i' \in I_b} \delta_{i,i'} C_{i,i',t'} \right) \quad (3)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t' \leq \Delta t + t, t \neq |T|$$

$$T_{t'} - T_t \leq H \left(1 - \sum_{i \in I_{zw}} \sum_{l \in L_i} \mu_{i,r}^{p} N_{i,l,t,t'} \right) + \sum_{i \in I_{zw}} \mu_{i,r}^{p} \left(\sum_{l \in L_i} (\alpha_i N_{i,l,t,t'} + \beta_i \xi_{i,l,t,t'}) + \sum_{i' \in I_{zw}} \delta_{i,i'} C_{i,i',t'} \right) \quad (4)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t' \leq \Delta t + t, t \neq |T|$$

$$T_{t'} - T_t \geq \sum_{i \in I_c} \mu_{i,r}^{p} \left(\sum_{l \in L_i} \frac{\xi_{i,l,t,t'}}{\rho_i^{max}} + \sum_{i' \in I_c} \delta_{i,i'} C_{i,i',t'} \right) \quad (5)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t' \leq t + 1, t \neq |T|$$

$$T_{t'} - T_t \leq H \left(1 - \sum_{i \in I_{mr}} \sum_{l \in L_i} \mu_{i,r}^{p} N_{i,l,t,t'} \right) + \sum_{i \in I_{mr}} \mu_{i,r}^{p} \left(\sum_{l \in L_i} \frac{\xi_{i,l,t,t'}}{\rho_i^{min}} + \sum_{i' \in I_{mr}} \delta_{i,i'} C_{i,i',t'} \right) \quad (6)$$

$$\forall r \in E \backslash E_{st}, t \in T, t' \in T, t < t' \leq t + 1, t \neq |T|$$

Furthermore, it is considered that during the planning horizon a set of multiple demand points $d \in D$ must be satisfied. A similar approach has been followed by Maravelias and Grossmann (2003). The binary variable $Y_{t,d}$ is defined to identify whether a specific event point t corresponds to a demand points d. Here, it is assumed that each event point t, $t \neq 1$, has to be associated with one due date d (equation 7). When those events matches, the absolute time T_t must be equal to the specified due time h_d, which is assured by equations 8 and 9.

$$\sum_{\substack{t \in T \\ t \neq 1}} Y_{t,d} = 1 \qquad \forall\, d \in D \quad (7)$$

$$T_t \geq \sum_{d \in D} h_d Y_{t,d} \qquad \forall t \in T, t \neq 1 \qquad (8)$$

$$T_t \leq \sum_{d \in D} h_d Y_{t,d} + H\left(1 - \sum_{d \in D} Y_{t,d}\right) \qquad \forall t \in T, t \neq 1 \qquad (9)$$

Finally, equation 10 assures that no time events have the same absolute value and these timing variables are bounded by equations 11a and 11b, considering the time horizon interval given by $[0, H]$.

$$T_{t+1} - T_t \geq 1 \qquad \forall t \in T, t \neq |T| \qquad (10)$$

$$T_1 = 0 \qquad (11a)$$

$$T_{|T|} \leq H \qquad (11b)$$

3.2.3 Resource balance constraints

The resource balance equation states that the excess amount at a specific event point t is equal to the amount at the previous event point. For t=1, this value refers to the initial availability $R^0_{r,l}$, adjusted by the amounts discretely or continuously consumed/produced by all tasks starting or ending a time event t. Constraints for materials resources (set M) of lot l (equations 12-15) are modelled separately from equipment units (set E) (equation 16).

Equation 12 stresses the general balance for all material resources $r \in M$, where $R_{r,l,t}$ characterises the excess resource r availability of lot l and time point t. In addition to the initial or previous term of the balance, $R^p_{r,l,t}$ and $R^c_{r,l,t}$ represents the amount produced and consumed, respectively. The variable $W_{r,l,t}$ is related to the waste disposal amount when resource shelf-life is exceeded and $\Pi_{r,l,t}$ to the amount expedited at a corresponding due date. The variables $R^c_{r,l,t}$ and $\Pi_{r,l,t}$ are considered negative in the balance.

The amount of material produced is formulated through equation 13, where the first term is related to batch tasks and the second to continuous tasks that produce resource r of lot $l \in L_r$. Likewise, equations 14 and 15 formulate the material consumption. However, the latter equation extends the feature of blending lots of stable intermediaries or products to originate other lots of intermediaries or final products (Moniz et al., 2014a). It addresses the consumption balance for a set L^r_B of lots of resource $r \in B$ that are able to be blended, allowing the tracking of the blending process.

$$R_{r,l,t} = R^0_{r,l}|_{t=1} + R_{r,l,t-1}|_{t>1} + R^p_{r,l,t} + R^c_{r,l,t} - W_{r,l,t} + \Pi_{r,l,t} \qquad \forall r \in M, l \in L_r, t \in T \qquad (12)$$

$$R^p_{r,l,t} = \sum_{i \in I_b} \sum_{\substack{t' \in T \\ t - \Delta t \leq t' < t}} v^p_{i,r} \xi_{i,l,t',t} + \sum_{i \in I_c} \sum_{\substack{t' \in T \\ t-1 \leq t' < t}} \lambda_{i,r} \xi_{i,l,t',t} \qquad \forall r \in M, l \in L_r, t \in T \qquad (13)$$

$$R^c_{r,l,t} = \sum_{i \in I_b} \sum_{\substack{t' \in T \\ t < t' \le t + \Delta t}} v^c_{i,r} \xi_{i,l,t,t'} + \sum_{i \in I_c \setminus I^c_{rBC}} \sum_{\substack{t' \in T \\ t-1 \le t' < t}} \lambda_{i,r} \xi_{i,l,t',t} + \sum_{i \in I^c_{rBC}} \sum_{\substack{t' \in T \\ t < t' \le t+1}} \lambda_{i,r} \xi_{i,l,t,t'} \quad (14)$$

$$\forall r \in M \setminus B, l \in L_r, t \in T$$

$$\sum_{l \in L^r_B} R^c_{r,l,t} = \sum_{l \in L^r_B} \left(\sum_{i \in I_b} \sum_{\substack{t' \in T \\ t < t' \le t + \Delta t}} v^c_{i,r} \xi_{i,l,t,t'} + \sum_{i \in I_c \setminus I^c_{rBC}} \sum_{\substack{t' \in T \\ t-1 \le t' < t}} \lambda_{i,r} \xi_{i,l,t',t} + \sum_{i \in I^c_{rBC}} \sum_{\substack{t' \in T \\ t < t' \le t+1}} \lambda_{i,r} \xi_{i,l,t,t'} \right) \quad (15)$$

$$\forall r \in B, t \in T$$

As previously mentioned, it is considered that only consecutive continuous tasks can occur simultaneously in the same time schedule $[t, t']$ (in different equipment units) and the formulation should restrict the schedule of any other combinations. Albeit, the tests performed to the baseline formulation by Castro et al. (2004) verifies all tasks combinations except one: an additional term is required to assure that when a continuous task consumes the intermediate material r produced by a batch task (subset I^c_{rBC}), that occurs in different time intervals, which is guaranteed by the last term of equations 14 and 15. To further explain this feature, in Figure 3 is schematised a generic production process of product D composed by a set of three tasks: the first as a batch task TB ($1 \times A \rightarrow 1 \times B$) followed by two continuous steps, TC1 ($1 \times B \rightarrow 1 \times C$) and TC2 ($1 \times C \rightarrow 0.5 \times D$). For simplification, lets consider the main balance equations for material resources (Equation 12-14), assuming that all tasks can last only a single time interval (Δt =1) and disregarding all aspects related to the lot features. Considering two demand dates for product D (50kg @21 hours and 60kg @33 hours), the Gantt chart shows the sequence of scheduled tasks to fulfil that deliveries ($\Pi_{D,l,3}$, $\Pi_{D,l,4}$). But as can be noticed, to accurately calculate the balance for intermediate materials B and C, it cannot be based on the same "consumption" term of the equation, as the original formulation suggests. With this reformulation is guaranteed, through the term applied to the set of tasks I^c_{rBC}, that if material B is produced (at TB) in interval $[t-1, t]$, it is only consumed (at TC1) in the following interval $[t, t+1]$. In the case of material C, since it is used by two consecutive continuous tasks, its production and consumption can occur on the same time interval $[t-1, t]$.

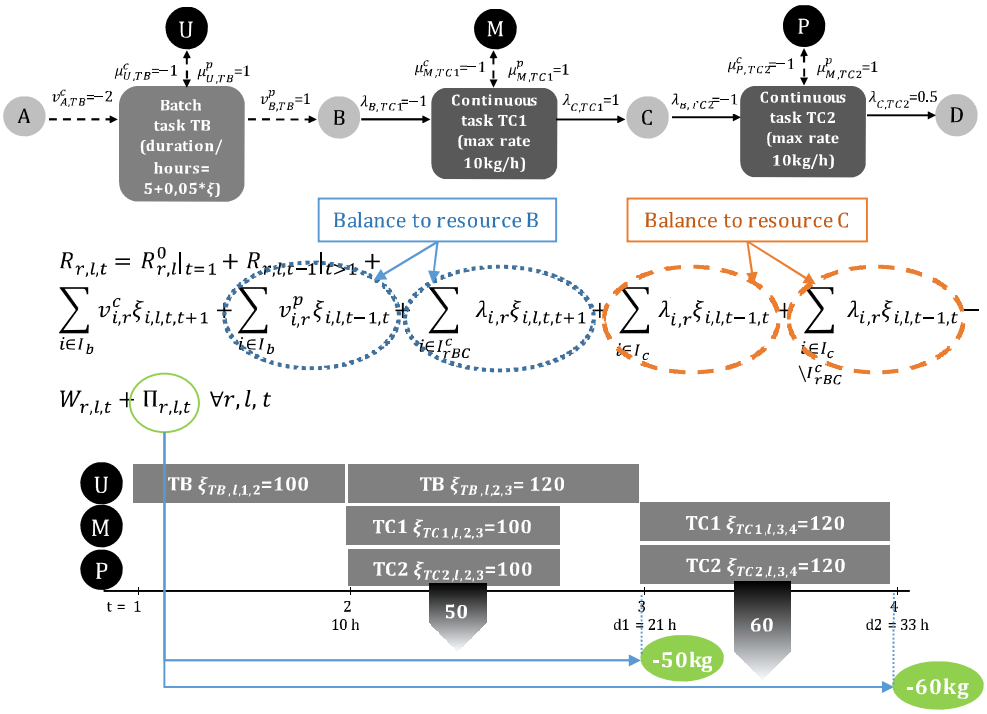

Figure 3 – Representation of process modelling formulation (material resource balance)

The resource balance constraints to equipment resources E is presented in equation 16. Here, the index l in the balance variable $R_{r,t}$ is dropped since the lot traceability is only required for material resources. The initial terms of equation 16 follow the same resource availability concerning the occurrence of batch and/or continuous tasks that take place in the boundaries of the time event. The last term refers to the set of storage tasks of each material resource/lot ($i \in I_{st}$). This equation assumes that all equipment resources are considered individually, with exception of storage tanks ($r \in E_{st}$) which are considered a group of entities available ($R_r^{init} > 1$), assigned for each product storage when required.

$$
\begin{aligned}
R_{r,t} = R_r^0|_{(t=1)} + R_{r,t-1}|_{t>1} \\
+ \sum_{i\in I_b}\sum_{l\in L_r}\left(\sum_{\substack{t'\in T \\ t-\Delta t\le t'<t}}\left(\mu_{i,r}^p N_{i,l,t',t}\right) + \sum_{\substack{t'\in T \\ t<t'\le t+\Delta t}}\left(\mu_{i,r}^c N_{i,l,t,t'}\right)\right) \\
+ \sum_{i\in I_c}\sum_{l\in L_r}\left(\sum_{\substack{t'\in T \\ t-1\le t'<t}}\left(\mu_{i,r}^p N_{i,l,t',t}\right) + \sum_{\substack{t'\in T \\ t<t'\le t+1}}\left(\mu_{i,r}^c N_{i,l,t,t'}\right)\right) \\
+ \sum_{i\in I_{st}}\sum_{l\in L_r}\left(\mu_{i,r}^p N_{i,l,t-1,t} + \mu_{i,r}^c N_{i,l,t,t+1}\right) \\
\forall r \in E, t \in T
\end{aligned}
\tag{16}
$$

Equation 17 performs the initial assignment of the equipment units E, considering processing and storage units, and equation 18 bounds the allowed resource availabilities. Equation 19 guarantees that, when applied, no material resource other than the raw materials (RM) is allowed be stored at the last event of the time horizon. This restriction is particularly useful to access the case that products/by-products cannot be stored beyond the planning horizon due to shelf-life restrains.

$$R_r^0 \leq R_r^{init} \qquad \forall\, r \in E \qquad (17)$$

$$0 \leq \sum_{l \in L_r} R_{r,l,t} \leq R_r^{max} \qquad \forall\, r \in M, t \in H \qquad (18)$$

$$\sum_{r \in M \setminus RM} \sum_{l \in L_r} R_{r,l,t} = 0 \qquad \forall\, t = |T| \qquad (19)$$

3.2.4 Lot constraints

According to Moniz et al. (2013), a distinction must be made in the formulation of lots and task–batches. Lots characterise the amount of stable intermediate or final product produced throughout a known set of tasks executed in a known production sequence or recipe. Task-batches are related to the amount of material produced by each task that is limited by the capacity of the processing unit, executing part of the production of a lot. In this way, the formulation addresses the ability to trace the proportions/quantities of all products lots in the production schedule, allowing the record of the processing of a certain lot (or a lot blend/split, if allowed) through the task-batching of raw materials, intermediate and final products.

Regarding the lot traceability of the produced materials, two additional constrains are considered to enhance the model features. Equations 20 and 21 states that, for either batch or continuous tasks, respectively, lot l is only executed if the lot l−1 was already assigned, in a previous time interval, to a task that can produce the same material resource (first subtracting term), or up to the same interval but in an alternative equipment unit (second subtracting term). Equation 22 allows that, if required, lot l of a material resource is never repeated during the planning horizon, which, when no limits are set to a predefined number of lots, allows the determination of the total number of lots required.

$$v_{i,r}^p N_{i,l,t,t'} - \sum_{\substack{t'' \in T \\ t'' \leq t}} \sum_{\substack{t''' \in T \\ t''-\Delta t \leq t''' < t''}} v_{i,r}^p N_{i,l-1,t''',t''} - \sum_{\substack{i' \in I_b \\ i' \neq i}} \sum_{\substack{t'' \in T \\ t'' \leq t'}} \sum_{\substack{t''' \in T \\ t''-\Delta t \leq t''' < t''}} v_{i,r}^p N_{i',l-1,t''',t''} \leq 0 \qquad (20)$$

$$\forall r \in M \setminus RM, i \in I_b, l \in L_r, l > 1, t \in T, t' \in T, t < t' \leq t + \Delta t, t \neq |T|$$

$$\lambda_{i,r} N_{i,l,t,t'} - \sum_{\substack{t'' \in T \\ t'' \leq t}} \sum_{\substack{t''' \in T \\ t''-1 \leq t''' < t''}} \lambda_{i,r} N_{i,l-1,t''',t''} - \sum_{\substack{i' \in I_c \\ i' \neq i}} \sum_{\substack{t'' \in T \\ t'' \leq t'}} \sum_{\substack{t''' \in T \\ t''-1 \leq t''' < t''}} \lambda_{i,r} N_{i',l-1,t''',t''} \leq 0 \qquad (21)$$

$$\forall r \in M \setminus RM, i \in I_c, l \in L_r, l > 1, t \in T, t' \in T, t < t' \leq t + 1, t \neq |T|$$

$$\sum_{i \in I_b} \sum_{\substack{t \in T \\ t \neq |T|}} \sum_{\substack{t'' \in T \\ t < t' \leq t + \Delta t}} v_{i,r}^p N_{i,l,t,t'} + \sum_{i \in I_c} \sum_{\substack{t \in T \\ t \neq |T|}} \sum_{\substack{t' \in T \\ t < t' \leq t+1}} \lambda_{i',r} N_{i',l,t,t'} \leq 1 \qquad (22)$$

$$\forall r \in M \setminus RM, l \in L_r$$

3.2.5 Multiple deliveries constraints

The multiple deliveries feature is modelled through equations 23 to 25. Equation 23a defines the multiple product/lot deliveries trough variable $\Pi_{r,l,t}$, with a set of due dates $d \in D$ and products P. The amount of resource r of one lot l at due date d can be bounded by minimum $Q^{min}_{r,l,d}$ and maximum quantities $Q^{max}_{r,l,d}$, while in each due date the unfulfilled minimum demand of product r of lot l is given by $\Pi^{u}_{r,l,t}$. Considering that, in our approach, the total number of lots l to schedule can be defined as an output solution, equation 23b accesses the same balance assuming a minimum demand profile for single product (combining all lots) per due date, $Q_{r,d}$. The formulation also allows that a delivery could occur in any time event of the planning horizon, besides the predefined due dates. Therefore, equation 24 guarantees that no early deliveries are allowed, as well as that the total demand of each product P is not exceeded. Finally, equation 25 assures that no deliveries exist for other resources than products P.

$$\sum_{d \in D_r} (Y_{t,d}\, Q^{min}_{r,l,d}) - \Pi^{u}_{r,l,t} \leq (-\Pi_{r,l,t}) \leq \sum_{d \in D_r} (Y_{t,d}\, Q^{max}_{r,l,d}) \qquad \forall\, r \in P, l \in L_r, t \in T, t > 1 \tag{23a}$$

$$\sum_{d \in D_r} (Y_{t,d}\, Q_{r,d}) - \sum_{l \in L_r} \Pi^{u}_{r,l,t} \leq \sum_{l \in L_r} (-\Pi_{r,l,t}) \qquad \forall\, r \in P, t \in T, t > 1 \tag{23b}$$

$$\sum_{l \in L_r} (-\Pi_{r,l,t}) \leq \sum_{\substack{t' \in T \\ t' \leq t}} \sum_{d \in D_r} (Y_{t',d}\, Q_{r,d}) - \sum_{\substack{t' \in T \\ t' < t}} \sum_{l \in L_r} \left(-\Pi_{r,l,t'}\right) \qquad \forall\, r \in P, t \in T, t > 1 \tag{24}$$

$$\Pi_{r,l,t} = 0 \qquad \forall\, r \in M/P, l \in L_r, t \in T \tag{25}$$

3.2.6 Operational constraints

Assuming that each task can be performed in a single processing unit, equation 26 accounts for equipment capacity restrains of batch tasks ($V^{min}_{i,l}$ and $V^{max}_{i,l}$). For continuous tasks, the boundaries are related to the processing rate and length of the interval (equation 27). In this case, the lower limit is defined by the minimum campaign length of the processing task i, set by parameter $Camp_{i,l}$, and the upper limit to the lifetime of the processed products at the same tasks $\sigma_{i,l}$. This last term reinforces that the product shelf life will never be exceeded during one single continuous task. If required, the same principle can be followed for a batch task by assuming a maximum capacity of the equipment suitable to comply with lifetime of processed materials.

$$V^{min}_{i,l} N_{i,l,t,t'} \leq \xi_{i,l,t,t'} \leq V^{max}_{i,l} N_{i,l,t,t'} \qquad \forall\, i \in I_b, l \in L_i, t \in T, t' \in T, t < t' < t + \Delta t, t \neq |T| \tag{26}$$

$$Camp_{i,l}\rho_i^{max}N_{i,l,t,t'} \leq \xi_{i,l,t,t'} \leq \sigma_{i,l}\rho_i^{max}N_{i,l,t,t'} \quad (27)$$
$$\forall\, i \in I_c, l \in L_i, t \in T, t' \in T, t < t' < t+1, t \neq |T|$$

3.2.7 Sequence dependent changeover constraints

The production schedule should also address the required cleaning procedures based on sequence dependent changeovers, considered in our formulation as an autonomous task. In biopharmaceutical processes the changeover task can usually include, besides the cleaning time, any setup time related to process start-up of the following production. For example, considering two consecutive tasks $\{i, i'\}$ of intermediaries products at the time event t, if the task i' processes a different product than i, it is required an intermediate changeover of the shared processing unit $(r \in E\backslash E_{st})$ to occur before the beginning of task i' with a specified duration $\delta_{i,i'}$. To avoid the increase in the number of scheduled time events, this task is implicitly allocated to the duration of one time interval in the boundary of t where the changeover is required. The novelty presented relies in the flexibility of the allocation to the previous time interval, assuming its performed immediately before t, or starting at the beginning of the following interval. As example, Figure 4 shows the two schedule possibilities for a general case of two products, A and B, able to be produced in the same unit, allowing the increase of the production output of B depending in the allocation of the required changeover task. This flexibility potentiates the objective function results and is particular relevant in single-time grid horizon formulations. Therefore, in equations 28 and 29, a binary variable $C_{i,i',t}$ is introduced to control the sequence of tasks $i \neq i'$ and allocation of the require intermediate changeover in the shared equipment, respectively for either batch or continuous task. The same variable is also required to associate a cost to these operations, further penalised in the objective function. However, this case is only verified for consecutive tasks in a time event, which implies to consider whenever empty time intervals exist in between two events ($t' > t$), adding a new term to equations 30 and 31 to access the changeover time in the boundaries of t'. Likewise, equations 32 and 33 address the set-up requirements for the first scheduled task on each equipment with the binary variable $C_{i,i,t}$. To avoid suboptimal solutions, equation 34 reinforces that in each time interval only one cleaning task takes place per equipment resource.

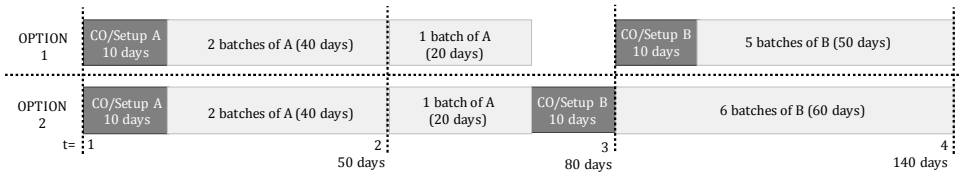

Figure 4 –Changeover tasks allocation options for a production case [A+B]

$$\sum_{l \in L_i} \sum_{\substack{t' \in T \\ t-\Delta t \leq t' < t}} \mu_{i,r}^{p} N_{i,l,t',t} + \sum_{l \in L_{i'}} \sum_{\substack{t' \in T \\ t < t' \leq t+\Delta t}} \mu_{i',r}^{p} N_{i',l,t,t'} \leq 1 + \mu_{i,r}^{p} C_{i,i',t} + \mu_{i,r}^{p} C_{i,i',t+1} \quad (28)$$
$$\forall r \in E\backslash E_{st}, i \in I_b\ , i' \in I_b\ , i' \neq i, t \in T, t > 1, t \neq |T|$$

$$\sum_{l\in L_i}\sum_{\substack{t'\in T\\ t-1\le t'<t}}\mu^p_{i,r}N_{i,l,t',t}+\sum_{l\in L_{i'}}\sum_{\substack{t'\in T\\ t<t'\le t+1}}\mu^p_{i',r}N_{i',l,t,t'} \le 1+\mu^p_{i,r}C_{i,i',t}+\mu^p_{i,r}C_{i,i',t+1} \quad \forall r\in E\backslash E_{st}, i\in I_c\ , i'\in I_c\ , i'\neq i, t\in T, t>1, t\neq |T| \tag{29}$$

$$\sum_{l\in L_i}\sum_{\substack{t''\in T\\ t-\Delta t\le t''<t}}\mu^p_{i,r}N_{i,l,t'',t}+\sum_{l\in L_{i'}}\sum_{\substack{t''\in T\\ t'<t''\le t'+\Delta t}}\mu^p_{i',r}N_{i',l,t',t''}-\sum_{i''\in I_b}\sum_{l\in L_{i''}}\sum_{\substack{t''\in T\\ t\le t''<t'}}\sum_{\substack{t'''\in T\\ t''<t'''\le t''+\Delta t}}\mu^p_{i'',r}N_{i'',l,t'',t'''} \le 1+\mu^p_{i,r}C_{i,i',t'}+\mu^p_{i,r}C_{i,i',t'+1} \quad \forall r\in E\backslash E_{st}, i\in I_b\ , i'\in I_b\ , i'\neq i, t\in T, t'\in T, t>1, t'>t, t\neq |T|, t'\neq |T| \tag{30}$$

$$\sum_{l\in L_i}\sum_{\substack{t''\in T\\ t-1\le t''<t}}\mu^p_{i,r}N_{i,l,t'',t}+\sum_{l\in L_{i'}}\sum_{\substack{t''\in T\\ t'<t''\le t'+1}}\mu^p_{i',r}N_{i',l,t',t''}-\sum_{i''\in I_c}\sum_{l\in L_{i''}}\sum_{\substack{t''\in T\\ t\le t''<t'}}\sum_{\substack{t'''\in T\\ t''<t'''\le t''+1}}\mu^p_{i'',r}N_{i'',l,t'',t'''} \le 1++\mu^p_{i,r}C_{i,i',t'}+\mu^p_{i,r}C_{i,i',t'+1} \quad \forall r\in E\backslash E_{st}, i\in I_c\ , i'\in I_c\ , i'\neq i, t\in T, t'\in T, t>1, t'>t, t\neq |T|, t'\neq |T| \tag{31}$$

$$\sum_{l\in L_i}\sum_{\substack{t'\in T\\ t<t'\le t+\Delta t}}\mu^p_{i,r}N_{i,l,t,t'}-\sum_{i'\in I_b}\sum_{l\in L_{i'}}\sum_{\substack{t'\in T\\ t'\le t}}\sum_{\substack{t''\in T\\ t'-\Delta t\le t''<t'}}\mu^p_{i',r}N_{i',l,t'',t'}\Big|_{t>1} \le \mu^p_{i,r}C_{i,i,t+1}+\mu^p_{i,r}C_{i,i,t}\big|_{t>1} \quad \forall r\in E\backslash E_{st}, i\in I_b\ , t\in T, t\neq |T| \tag{32}$$

$$\sum_{l\in L_i}\sum_{\substack{t'\in T\\ t<t'\le t+1}}\mu^p_{i,r}N_{i,l,t,t'}-\sum_{i'\in I_c}\sum_{l\in L_{i'}}\sum_{\substack{t'\in T\\ t'\le t}}\sum_{\substack{t''\in T\\ t'-1\le t''<t'}}\mu^p_{i',r}N_{i',l,t'',t'}\Big|_{t>1} \le \mu^p_{i,r}C_{i,i,t+1}+\mu^p_{i,r}C_{i,i,t}\big|_{t>1} \quad \forall r\in E\backslash E_{st}, i\in I_c\ , t\in T, t\neq |T| \tag{33}$$

$$\sum_{i\in I_b\cup I_c}\sum_{\substack{i'\in I_b\cup I_c\\ i'\neq i}}\mu^p_{i,r}C_{i,i',t} \le 1 \quad \forall r\in E\backslash E_{st}, t\in T, t>1, t\neq |T| \tag{34}$$

3.2.8 Storage and shelf-life constraints

Considering a set of storage tasks for each intermediaries and final products $I_{st}=I^B_{st}\cup I^C_{st}$ and a set of storage equipment resources $r\in E_{st}$, the model should

constraint the stored products to shelf-life time restrains. Shelf-life must be considered as the maximum lifetime a product/by-product is able to be stored ($\sigma_{i,l}$), sending to waste disposal the respective amounts when this parameter is exceed. Equations 35 to 37 control the activation of a storage task in the boundary intervals if there is an excess amount at event point *t* of the material resource *r* of lot *l.* Due to the different processing mode of tasks, it is considered that for materials produced by batch tasks, the storage task I_{st}^{B} must be activate only to the ensuing interval $[t,\ t+1]$. Instead, the storage of materials produced by continuous tasks, I_{st}^{C}, must be activate on both intervals, $[t-1\ ,t]$ and $[t,\ t+1]$, since it is assumed that the material is processed continuously from the start of the interval. Additionally, in the case of intermediaries consumed by continuous tasks, the storage task $I_{st}^{INT\_C}$ task must be active on $[t+1,\ t+2]$.

$$V_{i,l}^{min} N_{i,l,t,t+1} \leq \sum_{r \in I_r^{st}} R_{r,l,t} \leq V_{i,l}^{max} N_{i,l,t,t+1} \quad \forall\, i \in I_{st}^{B} \cup I_{st}^{C}, l \in L_i, t \in T, t \neq |T| \tag{35}$$

$$V_{i,l}^{min} N_{i,l,t-1,t} \leq \sum_{r \in I_r^{st}} R_{r,l,t} \leq V_{i,l}^{max} N_{i,l,t-1,t} \quad \forall\, i \in I_{st}^{C}, l \in L_i, t \in T, t \neq 1 \tag{36}$$

$$V_{i,l}^{min} N_{i,l,t+1,t+2} \leq \sum_{r \in I_r^{st}} R_{r,l,t} \leq V_{i,l}^{max} N_{i,l,t+1,t+2} \quad \forall\, i \in I_{st}^{INT\_C}, l \in L_i, t \in T, t \neq 1 \tag{37}$$

To accurately control the shelf-life of stored materials, and since each storage task ($i \in I_{st}$) is activated for the entire time interval, the variable $x_{i,l,t,t'}$ is introduced to control the storage time of the corresponding material resource *r* of lot *l.* As example, the variable $x_{i,l,t,t+1}$ should account as storage time the value of the time period [*t,t+1*], given by $(T_{t+1} - T_t)$, only if the storage task is active in that interval, $N_{ilt(t+1)} = 1$, otherwise is zero. Therefore, since $(T_{t+1} - T_t) > 0$, $\forall\, t \in T$, the master constraint could be given by the multiplication these two variables, $x_{ilt(t+1)} \equiv N_{ilt(t+1)} \cdot (T_{t+1} - T_t)$, however generating a nonlinear function. Assessing the singularity of the MILP model, equations 38 to 40 formulates the linearization of this proposition for the interval [*t,t'*].

$$x_{i,l,t,t'} - H \sum_{\substack{t'' \in T \\ t \leq t'' < t'}} N_{i,l,t'',t''+1} \leq 0 \quad \forall\, i \in I_{st}, l \in L_i, t \in T, t' \in T, t' > t, t \neq |T| \tag{38}$$

$$x_{i,l,t,t'} \leq (T_{t'} - T_t) \quad \forall\, i \in I_{st}, l \in L_i, t \in T, t' \in T, t' > t, t \neq |T| \tag{39}$$

$$x_{i,l,t,t'} \geq (T_{t'} - T_t) - H \left((t' - t) - \sum_{\substack{t'' \in T \\ t \leq t'' < t'}} N_{i,l,t'',t''+1} \right) \quad \forall\, i \in I_{st}, l \in L_i, t \in T, t' \in T, t' > t, t \neq |T| \tag{40}$$

If a sequence of storage tasks associated with a material resource r of lot l have extended the product lifetime σ_{il} a binary variable $S_{i,l,t,t'}$is activated (equations 41 and 42). To assure the feasibility, it is assumed that the shelf-life related to any intermediate/product is never greater that the considered time horizon H.

$$x_{i,l,t,t'} - \sigma_{i,l} \leq HS_{i,l,t,t'} \qquad \forall\, i \in I_{st}, l \in L_i, t \in T, t' \in T, t' > t, t \neq |T| \tag{41}$$

$$x_{i,l,t,t'} - \sigma_{il} \geq H(S_{i,l,t,t'} - 1) \qquad \forall\, i \in I_{st}, l \in L_i, t \in T, t' \in T, t' > t, t \neq |T| \tag{42}$$

Equations 39 and 40 guarantee that, for an interval [t,t'], if the stored resource r of lot l has extended the product lifetime ($S_{i,l,t,t'} = 1$), the variable W_{rlt} determines the respective amount sent to waste disposal ($R_{r,l,t'-1}$). $V_{st}^{max}$is a big-M scalar related to the overall maximum available storage capacity. Finally, equations 43 and 46 assures that variable $W_{r,l,t}$ take value zero for all the remaining cases where no shelf life restrains are applied.

$$W_{r,l,t'} \geq R_{r,l,t'-1} - V_{st}^{max}\left(1 - \sum_{i \in I_r^{st}} S_{i,l,t,t'}\right) \qquad \forall\, r \in M/RM, l \in L_r, t \in T, t < |T| - 1, t' > t + 1 \tag{43}$$

$$W_{r,l,t'} \leq R_{r,l,t'-1} + V_{st}^{max}\left(1 - \sum_{i \in I_r^{st}} S_{i,l,t,t'}\right) \qquad \forall\, r \in M/RM, l \in L_r, t \in T, t < |T| - 1, t' > t + 1 \tag{44}$$

$$W_{r,l,t'} \leq V_{st}^{max} \sum_{i \in I_r^{st}} S_{i,l,t,t'} \qquad \forall\, r \in M/RM, l \in L_r, t \in T, t < |T| - 1, t' > t \tag{45}$$

$$\sum_{t \in T} W_{r,l,t} = 0 \qquad \forall\, r \notin M/RM, l \in L_r \tag{46}$$

3.2.9 Objective function

Regarding the objective function, the profit maximisation is given by equation 47. The first term represents the income result from sales (v_r) minus the production costs (c_r), the second and third term represents the operating costs due to an active storage request for the excess amount of resource r at each time event (c_r^{st}) and the cost of intermediate changeover/setup-up procedures required in-between different tasks *i* and *i*' ($c_{i,i'}^{ch}$), and the last terms are related to the disposal cost (c_r^d) of extended shelflife products and backlog penalties cost (c_r^u) of unfulfilled demand. All costs are in "relative monetary units" (rmu).

$$max\left[\sum_{r\in P}\sum_{l\in L_r}\sum_{t\in T,t>1}(v_r-c_r)(-\Pi_{r,l,t})\right.$$
$$-\sum_{r\in M_{st}}\sum_{l\in L_r}\sum_{t\in T}(c_r^{st}R_{r,l,t})-\sum_{i\in I_r}\sum_{\substack{i'\in I_r\\ i'\neq i}}\sum_{l\in L_i}(c_{i,i'}^{ch}C_{i,i',t}) \quad (47)$$
$$\left.-\sum_{r\in M/RM}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}}c_r^dW_{r,l,t}-\sum_{r\in P}\sum_{l\in L_r}\sum_{\substack{t\in T\\ t>1}}c_r^u\Pi_{r,l,t}^u\right]$$

4 ILLUSTRATIVE EXAMPLES

In this section, considering the mathematical formulation composed by equations 3 to 47, three planning/scheduling optimisation problems in a biopharmaceutical industrial plant are presented to explore the different model features. The examples were adapted from the operational parameters provided by Lakhdar et al. (2005), which is based on real industrial data and covering the most common aspects of biopharmaceuticals' production. All models were implemented using GAMS (GAMS 24.4.3 WIN VS8 x86) and solved with CPLEX running on an Intel Xeon ES-2660 v3 at 2.60 GHz with 64 GB of RAM.

4.1 Example I

The first example considers a mid-term planning problem in the biopharmaceutical industry adapted from Lakhdar et al. (2005): a two-stages facility composed by two upstream fermentation suites [J1 & J2] and two downstream purification suites [J3 & J4] per stage, to manufacture products P1, P2 and P3 in a continuous production mode (Figure 5). The demand profile considers a total of 34 batches to be delivered in a set of campaign-lots in five delivery dates for a 360 days production horizon H (Table 1), assuming that late deliveries are penalised. For the profit maximisation, the problem considers: the total sales and the costs of manufacturing, storage, changeover/setup and disposal. The time related to sequence independent changeover/setup procedures was determined based in the product lead time provided in the example by Lakhdar et al. (2005). The remaining data used in the formulation, including manufacturing rate, minimum campaign length and product lifetime, is summarised in Tables 2a and 2b. The term "batch" in the data parameter, in order to reproduce the original problem statement, was assumed to correspond to a fix undisclosed amount due to confidentiality reasons. To comply with processes requirements, the blending of lots of intermediates is allowed (equation 15), the changeovers in downstream units are set to occur only at the beginning of the time interval (equations 29 and 31), the given production rates corresponds to equipment maximum specs, and unlimited storage capacity is assumed with no zero wait policies. Furthermore, in order to compare the the results obtained by Lakhdar et al. (2005), the scheduled batch tasks are set to last only one time interval ($\Delta t = 1$) and restrictive storage constraints given by equations 36 and 37 were disregarded.

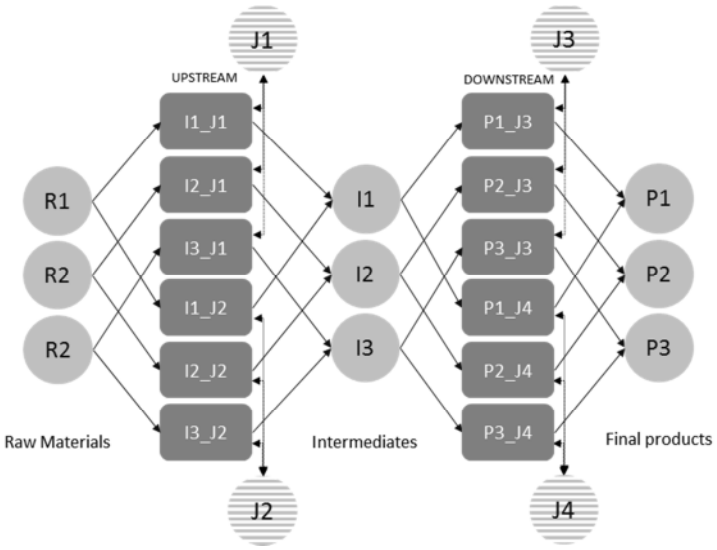

Figure 5 – RTN production layout for Example I

Table 1 – Demand profile for Example I

Product	**Total Demand (batch)**	**Due dates (days)**				
		d1 120	d2 180	d3 240	d4 300	d5 360
P1	12			6		6
P2	6		6			
P3	16	8			8	

Table 2a – Main parameters for Example I

	Manufacturing rate - max (batch/day)	**Sequence-Dep. Changeover time (days)**			**Minimum campaign length (days)**	**Stored material lifetime (days)**	**Storage cost (rmu/ batch.event)**	**Waste disposal cost (rmu/ batch)**	**Changeover cost (rmu)**
		I1	I2	I3					
I1	0.05	(10)	10	10	20	60	5	5	1
I2	0.045	10	(10)	10	22	60	5	5	1
I3	0.08	10	10	(10)	12.5	60	5	5	1
		P1	P2	P3					
P1	0.1	(30)	32	24.5	10	180	1	5	1
P2	0.1	30	(32)	24.5	10	180	1	5	1
P3	0.1	30	32	(24.5)	10	180	1	5	1

Table 2b– Main parameters for Example I

	Manufacturing cost (2 steps) (rmu/ batch)	**Sales price (rmu/ batch)**	**Lateness penalty (rmu/ batch)**	**Production factor $\lambda_{i,r}$**
P1	4	20	20	1
P2	4	20	20	1
P3	4	20	20	1

4.1.1 Example I results

The computational results for the optimal schedule are presented in Table 3. Since in a continuous time formulation the number of time events must be defined based on the analysis of the problem, the first attempt considered 6 event points. This it is the minimum allowed by the model, since there are 5 delivery time events plus the initial time point t_0. Although, it was insufficient for the total on-time fulfilment of the plan (profit 278 rmu, mostly penalised by late deliveries), but with 7 event points the demand is totally satisfied without penalties or waste disposal costs, for an optimal profit of 513 rmu. The results for 8 and 9 event points are shown but without any solution improvement, which is coherent with the proposed stopping criteria to deliver the solution when the increment in the number of event points is not accompanied by an increment in the objective function. In practice, since equation 10 does not allow the repetition of absolute time events, the solution is forced to create additional time intervals which can incur in profit penalties.

Table 3 – GAMS model results

Event Points	Discrete variables	Total variables	Equations	Objective MILP	CPU (s)	Optimality Gap (%)
6	3931	5638	6649	278	1.8	0.0
7	5237	7361	8898	513	27.8	0.0
8	6723	9300	11459	513	390.1	0.0
9	8389	11455	14332	511	2142.5	0.0

Considering the 7 event points solution, the Gantt chart of Figure 6 presents the optimal sequencing and allocation of the different processing tasks in each of the processing suites, identifying: lot number and integer campaign size of each intermediate/product manufacturing task (amount in brackets); the changeover/set up requirements when different products are processed in the same unit (identified by [CO] symbol); and the products' storage allocation (identified by [S] symbol). Due to different processing rates, the tool developed to generate the Gantt chart considered that the end of each downstream task is never lower than the end of precursor upstream task. The results exhibit, for example, that 4 lots of I1 and 3 lots of P1 are produced: lot L3 of P1 ($P1^{L3}$) is scheduled in unit [J4] during the time event interval [300,360] by the blending of lots L3 and L4 of I1. Also, a single lot L1 of I1 scheduled to unit [J1] generates a single lot of $P1^{L1}$ in unit [J4] during time event interval [120,180]. In this last case, the amount of lot L1 of P1 produced is being stored till the third delivery date (d3) on the 240th day. Six storage tasks are active in the planning horizon to store 5 lots of final products (until the due dates are met) and 1 lot of intermediary product I3, which can be detailed in the production inventory profile in Figure 7. These charts also verify that, on the 240^{th} day, lot $P1^{L1}$ (stored since the previous interval) and the produced lot $P1^{L2}$ totals 6 bathes delivered (indicated with a triangle symbol) corresponding to the due date d3 demand. Recall that in this example, each storage task is only active for the following time interval when the material resource excess is verified, according to equation 35. Regarding equipment changeover tasks, ten transfer cleaning/set-up procedures are required. Following the original problem statement by Lakhdar et al. (2005), the same set-up time was assigned for each first campaign scheduled. As noted, the changeover time for the upstream

units are allocated as suitable to either the beginning or end of the time slots, allowing the improvement of the duration/size of production tasks scheduled. Considering the utilisation rate of each equipment suite for the given horizon, it is verified that the upstream process is the limiting step due to its higher processing times, obtaining a 80% and 96% utilisation rate in J1 and J2, respectively, while downstream suites J3 and J4 present 55% and 71% rate, respectively.

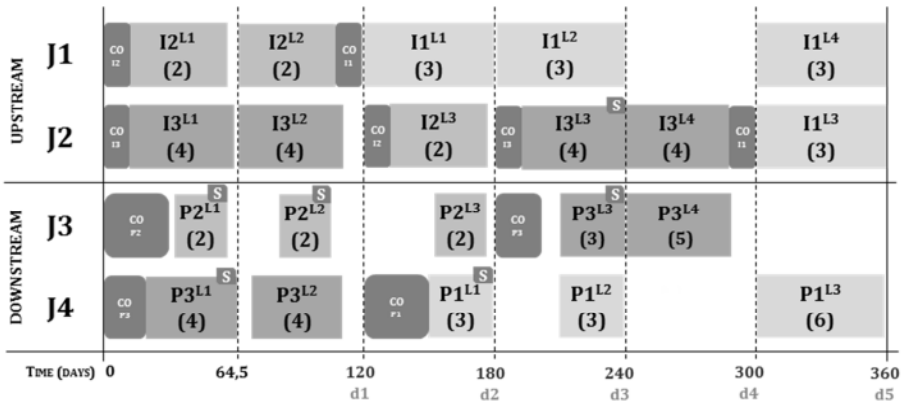

Figure 6 – Gantt chart for Example I (7 event points): e.g. L1 of I3 scheduled in time interval [0,64.5] to produce (4) batches; CO-changeover/set-up task assignment; S-storage allocation; d#-due date. (Solution: 513 rmu)

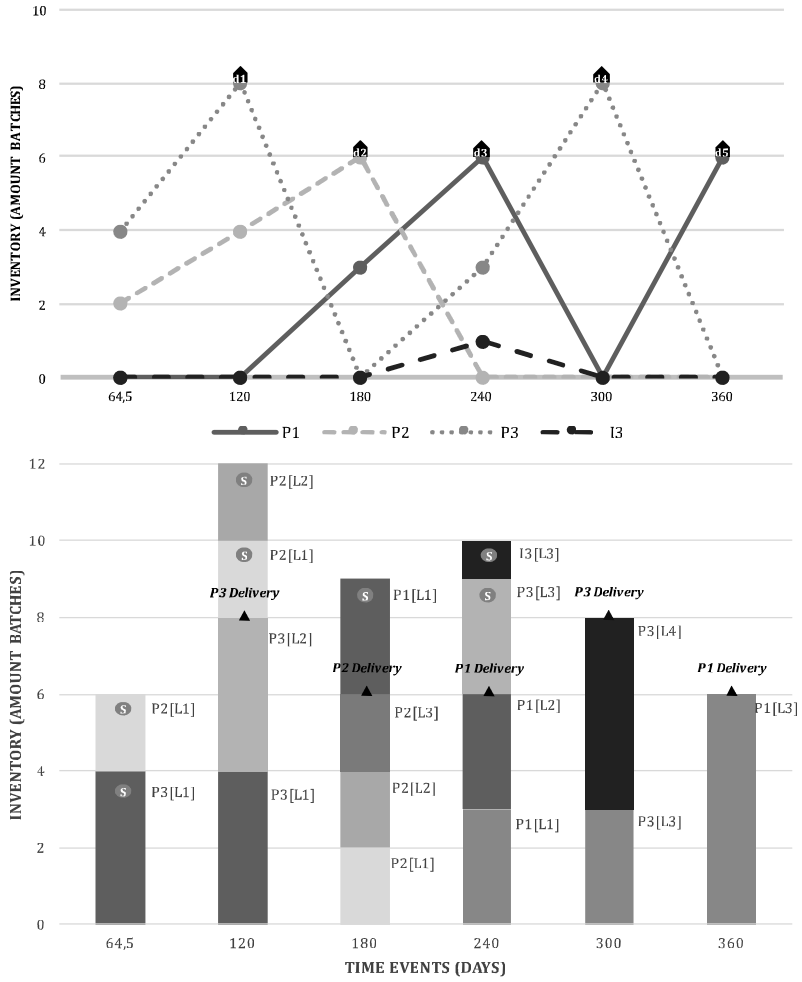

Figure 7 – Material resources inventory profile for Example I [(S] and [triangle] symbols identify, respectively, the storage allocation and the product amounts deliveries at due dates (d#))

4.1.2 Results comparison with Lakhdar et al. (2005) model

The mid-term planning problem here presented was originally addressed by Lakhdar et al. (2005), which proposed a MILP model with a 60 days discrete-time formulation to determine the optimal production schedule assuming a continuous processing upstream/downstream flow. The Gantt chart of Figure 8 and the production inventory profile in Figure 9 display the results obtained. In Table 4 the GAMS results are compared with our model solution with 7 event points in three distinct scenarios.

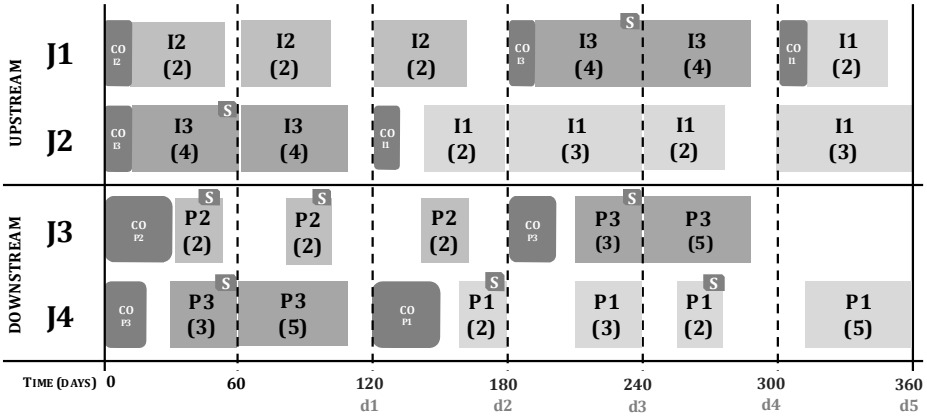

Figure 8 – Gantt chart for Example I using Lakhdar et al. (2005) discrete time formulation (Solution: 490 rmu)

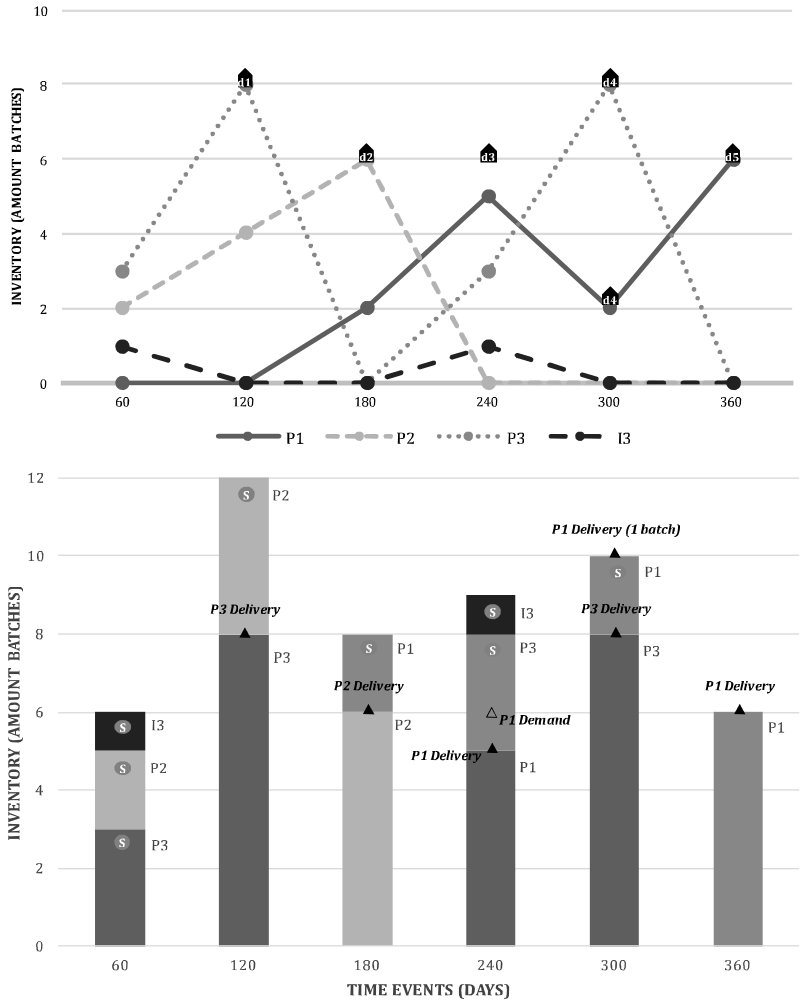

Figure 9 – Material resources inventory for Example I using Lakhdar et al. (2005) discrete time formulation

Table 4 – GAMS model results for Example I

	Discrete variables	Total variables	Equations	Objective MILP	CPU (s)	Optimality Gap (%)
Lakhdar et al. (2005)	252	457	499	490	0.3	0.0
Proposed model - 7 time events	5237	7361	8898	513	27.8	0.0
Proposed model for a single lot index - 7 time events	539	1601	2163	513	2.2	0.0
Proposed model using a continuous batch-extent variable - 7 time events	1709	7361	8898	519	46.9	0.0

The extent in number of variables and equations differ widely when comparing the discrete time model with our proposed continuous-time formulation, mostly due

to RTN framework and the additional features included, such as the lot tracking not addressed by Lakhdar et al. (2005). For a simplified comparison exercise of the two models, in Table 4 is also shown the solution statistics if the lot features were disregarded (constraints [20-22]), suggesting a significant reduction in computational complexity. Nevertheless, our solution schedule is able to provide an improved objective profit in +23 rmu (4.7%). The profit result of the discrete time model is mostly penalised by the unfulfilled delivery of 1 batch of P1 due at the 240th day (Figure 9). And although with one less changeover/set-up tasks scheduled, it presents additional storage costs of intermediate materials (I3 in the first and fourth time interval). Must be refereed that the discrete-time model presents a different estimate of the storage costs, but since both solutions show the same number of time intervals it can be disregarded. Indeed, the solution improvement is verified because the continuous-time model flexes the duration of the first time interval to 64.5 days (the remaining events were allocated to due dates), while the discrete-time model fixes all intervals length in 60 days, a time difference sufficient enough that allows to manufacture 4 batches of P3 in the first time slot to match demand on time. It was also verified that this model presents some limitations in the assignment of changeovers (demanding that at most one product undergoes manufacturing in any given intermediate time period) or in the implementation of a shorter discretization of the time horizon.

It must be noted that, to follow the original scheduling problem statement and perform a fair comparison with the results presented by Lakhdar et al. (2005), the extent variable $\xi_{illtt'}$ (that determines the amount of batches produced in each scheduled campaign-task) was also set as an integer variable. As expected, if the scheduling problem unrestraint the campaign-extent size to any non-integer number which, it can generate additional savings in the optimal profit by reducing the costs of stored products. Figure 10 illustrates this aspect, depicting a similar schedule solution but now the optimal profit increases to 519 rmu, mainly due to avoid the storage costs of intermediary I3. For example, the schedule of non-integer task campaigns allows that the amount stored of final products in t=120 days is equal to 3,7 batches (P2[L1&L2]), while in the previous solution the stored amounts is 4 batches.

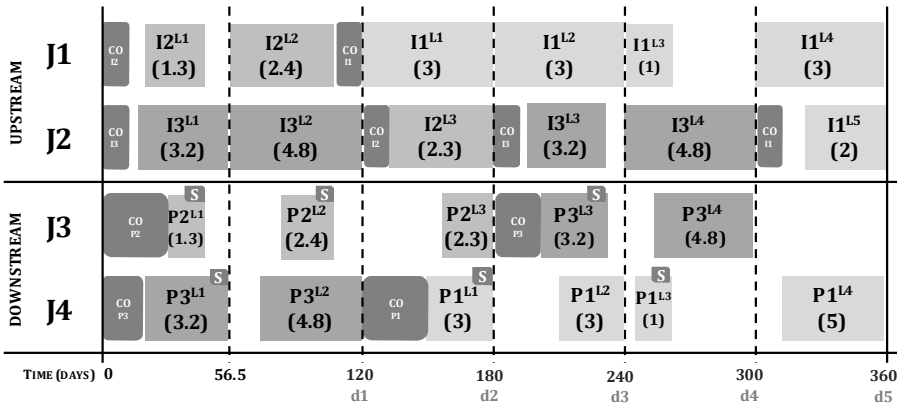

Figure 10 – Gantt chart for Example I (7 event points) considering the extent variable $\xi_{illtt'}$ as a positive continuous variable (Solution: 519 rmu)

4.2 Example II

To further demonstrate the model features, in this second example we are considering an alternative campaign planning problem for a shorter demand period of 240 days with three delivery dates, 6Kg of P1, 6Kg of P2 and 8Kg of P3, shown in Table 5. As displayed in Figure 11, the hybrid production process is now composed by one upstream stage that operates in a batch mode (Stage I), followed by two downstream continuous process steps, an ultrafiltration (Stage II) and a chromatography (Stage III) step, each stage composed by two identical processing suites. The operational data, presented in Table 6a and 6b, was adapted from provided industrial data. For this case, different sequence-dependent changeover times were defined for Stage 2 units for the process combinations possible (F1⇔F2⇔F3) and batch tasks are subject to equipment volume limitations. The same premises stated in Example I are followed, with the exception that the extent task variable $\xi_{iltt'}$ is not limited to integer amounts and all restrictions for storage tasks are applied (equations 36 and 37), which tightens the formulation for the lifetime limitations of biomaterials. Regarding the blending of lots of intermediaries, two situations are going to be explored, considering for the initial approach that all is allowed. Finally, based on a preliminary analysis of processing times, the maximum duration of all batch tasks was set to two time intervals ($\Delta t = 2$).

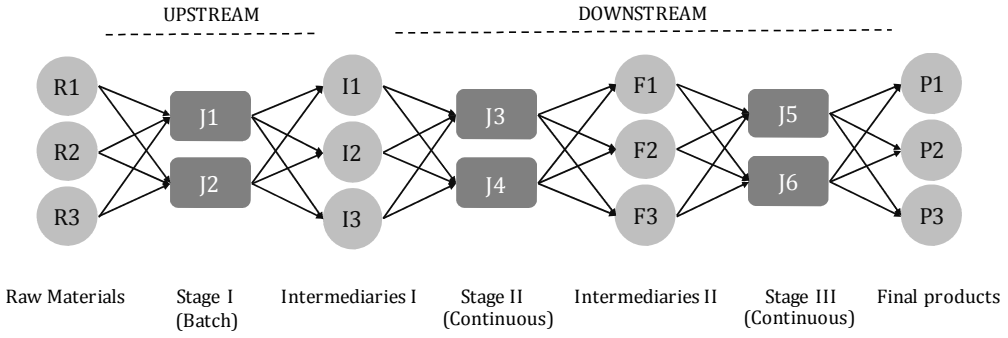

Figure 11 –Production layout for example II

Table 5 – Demand profile for Example II

Product	Total Demand (kg)	Due dates (days)		
		d1	d2	d3
		100	180	240
P1	6			6
P2	6		6	
P3	8	8		

Table 6a – Main parameters for Example II

	Manufacturing time – β (day/kg)	Sequence-dep. Changeover time (days)			Equipment capacity [max] (kg)	Stored material lifetime (days)	Storage cost (rmu/ kg.event)	Waste disposal cost (rmu/ kg)	Changeover cost (rmu)
		I1	I2	I3					
I1	18	(10)	10	10	5	60	5	5	1
I2	20	10	(10)	10	5	60	5	5	1
I3	12.5	10	10	(10)	5	60	5	5	1
	Manufacturing rate – max (kg/day)				**Minimum campaign length (days)**				
		F1	F2	F3					
F1	0.22	(10)	35	20	4,5	120	1	5	1
F2	0.2	16	(10)	30	5	120	1	5	1
F3	0.25	18	22	(10)	4	120	1	5	1
		P1	P2	P3					
P1	0.2	(30)	32	24.5	5	120	1	5	1
P2	0,2	30	(32)	24.5	5	120	1	5	1
P3	0.2	30	32	(24.5)	5	120	1	5	1

Table 6b – Main parameters for Example II

	Manufacturing cost (3 steps) (rmu/kg)	Sales price (rmu/kg)	Lateness penalty (rmu/kg)	Production factor $\lambda_{i,r}$
P1	6	20	20	1
P2	6	20	20	1
P3	6	20	20	1

4.2.1 Example II results

Table 7 reveals the results of the solution iteration for a set of time events, which the optimal solution is verified with 7 events for a profit of 268 rmu, since with 8 events no solution improvement is verified. In the first iteration with 4 time events (three due dates plus the initial $t = 0$), the profit solution is highly penalised with unfulfilled demand costs, seeing that the short number of time intervals is even more noticeable with this example, since a sequence of a batch and a continuous task requires, at least, two time intervals to accomplish the production of a certain amount. Since tasks in stage I are processed in batch mode, the produced intermediaries are only made available for the following stage after the end of the task, while continuous tasks of stages II and III occur simultaneously. The optimal planning is presented in the Gantt chart of Figure 12, outlining the sequencing, allocation, storage and changeover requirements for the campaign lots in each of the processing suites. Twelve equipment changeover/setup tasks are required and only one storage task is active for P1. Figure 13 resumes the production profile of Stage I intermediaries and final products, fulfilling the total demand on predefined due dates. It can be verified that the optimal solution considers that campaigns $I2^{L1}$, $I2^{L2}$ and $I1^{L1}$ are scheduled to widen for two consecutive time intervals, a model feature that improves the flexibility of the solution results, while preserving

computational hindrance, with relevance for this type of single-time grid horizon approaches.

Table 7 – GAMS model results for Example II

Event Points	Discrete variables	Total variables	Equations	Objective MILP	CPU (s)	Optimality Gap (%)
4	5087	4210	5087	-121.1	0.5	0.0
5	1961	6059	7735	122.8	3.2	0.0
6	2565	8196	10851	214.6	39.8	0.0
7	3223	10621	14435	268.0	101.8	0.0
8	3935	13334	18487	268.0	1509.2	0.0
9	4701	16335	23007	267.0	3600.0	1.0

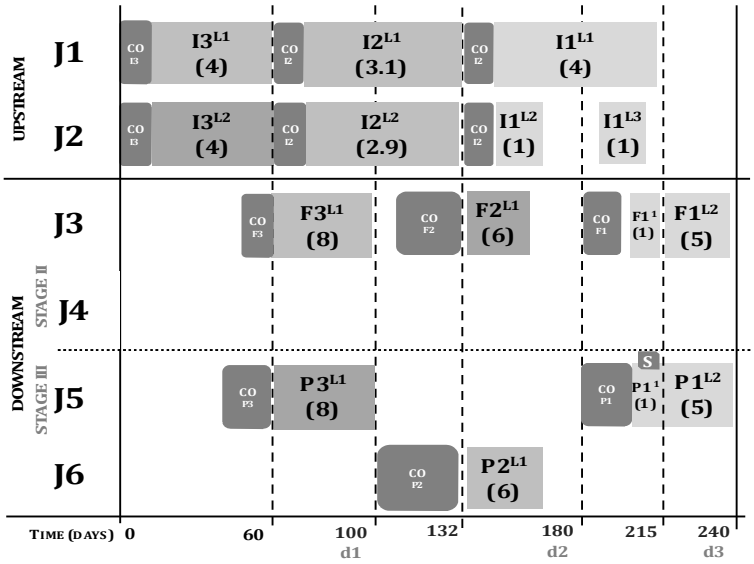

Figure 12 – Gantt chart for Example II with 7 event points (Solution: 268 rmu)

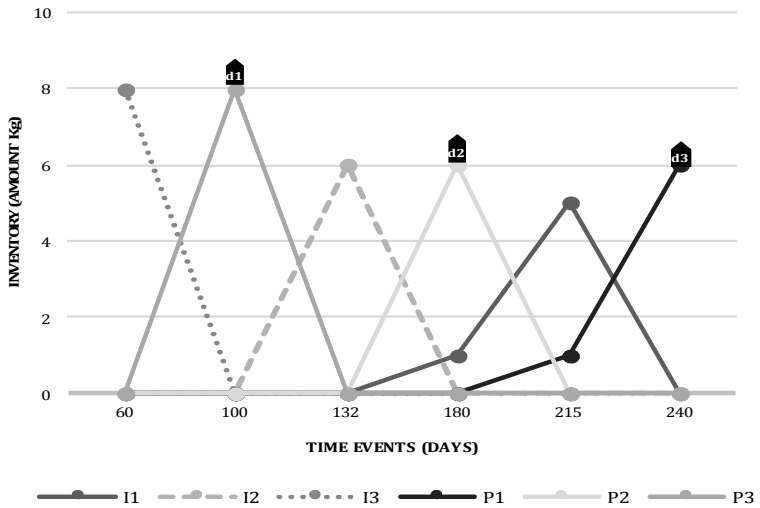

Figure 13 – Material resources inventory for Example II

It can be also verified in Figure 12 that suite J4 is not used, since the production rates in Stage II are sufficiently fast to process both Stage I lots of all intermediaries in the same unit. However, this is only possible because the blending/splitting of lots are allowed. Therefore, if we consider the case subject to regulatory purposes that the blending of Stage I intermediaries is forbidden (still allowed for intermediaries II), the new solution for 7 time events given in Figures 14 and 15 It can be verified that unit J4 is now required and it allows to follow the track record of the different lots throughout the units allocation of the production process. The optimal profit solution is now 265,3 rmu, penalised by the additional two changeover/set-up requirements and additional storage costs with $P1^{L1}$ at 218 days. As previously mentioned, the importance of regulatory requirements is strictly important in all aspects of pharmaceutical manufacturing, where the relevance of lot traceability plays an important role to comply with an optimal scheduling solution. As reference, in these examples it was assumed that the model freely assigns the number of sequential lots and sizes, but the formulation also allows the cases where a specific set of lot sizes are requested (equation 23a).

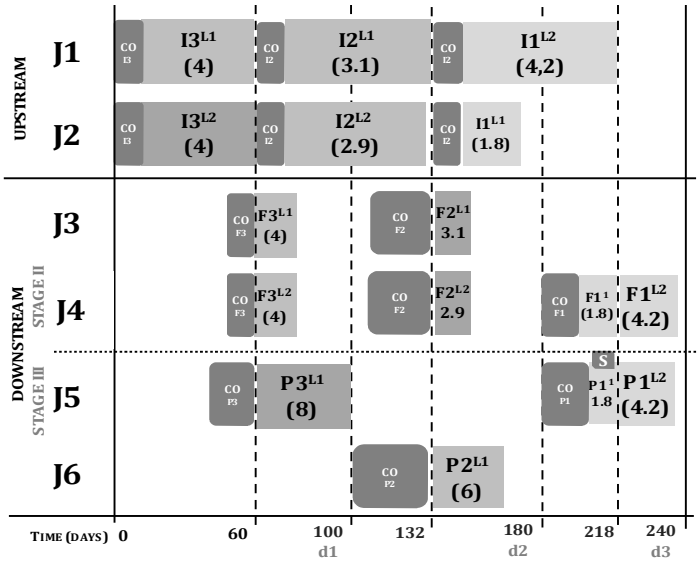

Figure 14 – Gantt chart for Example II with 7 event points, assuming no blending of Stage I intermediaries' lots (Solution: 265,3 rmu, 0% optimality gap, after 466s)

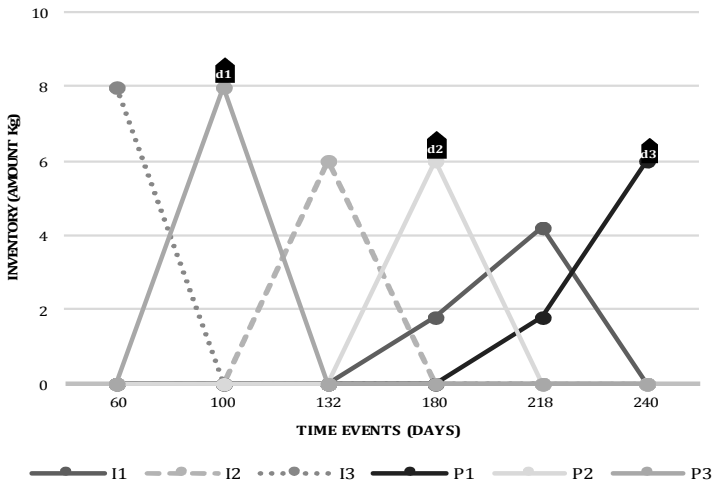

Figure 15 – Material resources inventory for Example II, assuming no blending of Stage I intermediaries' lots

4.3 Example III

In this third example, we address a more detailed process layout for the manufacturing of three biopharmaceutical products P1, P2 and P3, by disaggregating the upstream/downstream production suites into five main operations. The production sequence, as displayed in Figure 16, is composed by two batch stages for upstream processing (cell fermentation and clarification), and for downstream processing, the two first stages operate in a continuous mode while the last in batch mode (centrifugation, ultrafiltration and chromatography). The problem considers 9 equipment units and task-unit suitability is verified for intermediaries of P1 on the first upstream stage, as I1 can only be processed in unit J1 due to regulatory policies. In Table 8 is defined the demand profile with 3 due dates, and the remaining operational data, presented in Table 9a and 9b, was adapted from provided industrial data (different selling prices of final products were now considered). The same premises stated in Example II are followed, except that in this case the maximum duration of all batch tasks was assumed to last one interval ($\Delta t = 1$).

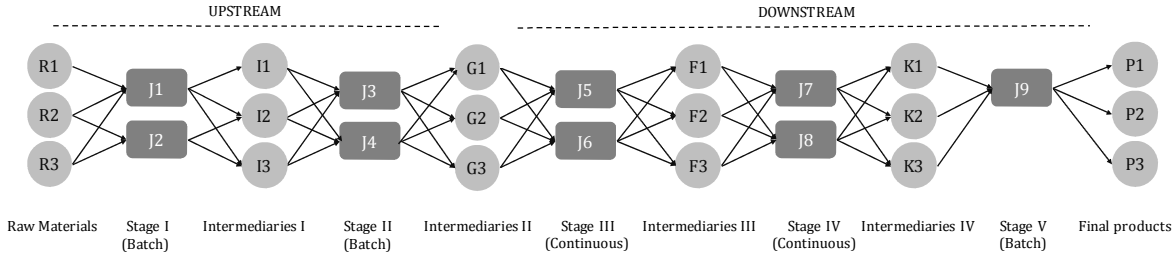

Figure 16 –Production layout for example III

Table 8 – Demand profile for Example III

Product	Total Demand (kg)	Due dates (days)		
		d1	d2	d3
		80	110	150
P1	2		2	
P2	2			2
P3	2	2		

Table 9a – Main parameters for Example III

	Manufacturing time – β (day/kg)	Sequence-dep. Changeover time (days)			Equipment capacity [max] (kg)	Stored material lifetime (days)	Storage cost (rmu/ kg.event)	Waste disposal cost (rmu/ kg)	Changeover cost (rmu)
		I1	I2	I3					
I1	10	(10)	10	10	5	60	5	5	1
I2	12	10	(10)	10	5	60	5	5	1
I3	6.5	10	10	(10)	5	60	5	5	1
		F1	F2	F3					
G1	5	(20)	3	20	4	120	5	5	1
G2	4	16	(20)	35	4	120	5	5	1
G3	4.5	18	22	(20)	4	120	5	5	1
	Manufacturing rate – max (kg/day)				Minimum campaign length (days)				
		F1	F2	F3					
F1	0.2	(15)	15	15	5	120	1	5	1
F2	0.25	15	(15)	15	5	120	1	5	1
F3	0.28	15	15	(15)	5	120	1	5	1
	Manufacturing rate – max (kg/day)				Minimum campaign length (days)				
		F1	F2	F3					
K1	0.32	(10)	18	18	5	120	1	5	1
K2	0.3	18	(10)	18	5	120	1	5	1
K3	0.28	18	18	(10)	5	120	1	5	1
	Manufacturing time – β (day/kg)	P1	P2	P3					
P1	6	(30)	32	24.5	5	120	1	5	1
P2	8	30	(32)	24.5	5	120	1	5	1
P3	4.5	30	32	(24.5)	5	120	1	5	1

Table 9b – Main parameters for Example III

	Manufacturing cost (5 steps) (rmu/kg)	Sales price (rmu/kg)	Lateness penalty (rmu/kg)	Production factor $\lambda_{i,r}$
P1	10	30	20	1
P2	10	38	20	1
P3	10	25	20	1

4.3.1 Example III results

With this industrial problem, the main goal was to discuss the model performance considering a production layout with a set of 5 process steps, acknowledging the generality of the model formulation with its different model features. In Table 8 is shown the solution iteration for each number of time events, to reach the optimal planning solution presented in the Gantt chart of Figure 17 (106 rmu for 8 time events). It shows the size/duration, sequencing, allocation, storage and changeover requirements for the campaign lots in each processing unit, with the flow sequence of batch and continuous tasks. Although, it requires additional time events to accomplish a complete production sequence, and for this reason, the first results of the solution iteration of Table 8 are

penalised. The profit results for 9 and 10 time events were also penalised due to extra storage costs. In the Gantt chart of Figure 17 is it possible to follow the schedule assignment of the different tasks and units throughout each production stage of intermediaries, able to comply with the deliver of two batches of each product on the 80th, 110th 150th day. It was assumed that the blending of lots in upstream stages was not allowed due to regulatory policies, but it can be verified at stage III, where two lots of F1 originate one of K1, as also the splitting of one lot of K2 to originate two lots of P2 at the final stage. The flexibility to schedule the changeover/set-up time and the blending of lots has proven to allow an improved allocation of the different tasks to the planning horizon. However, it was noted the computational complexity increase with the problem data set, which is a criterion in our research as a requirement to provide an operational decision-support tool for industrial environments.

Table 10 – GAMS model results for Example III

Event Points	Discrete variables	Total variables	Equations	Objective MILP	CPU (s)	Optimality Gap (%)
4	3318	7413	7877	-249	0.3	0.0
5	4443	12023	11483	-152	1.4	0.0
6	5658	16947	16263	- 41	4.9	0.0
7	6963	17727	22649	15	82.1	0.0
8	8358	22017	29129	106	95.2	0.0
9	9843	26733	36387	103	563.2	0.0
10	11418	31875	44423	101	1792.5	0.0

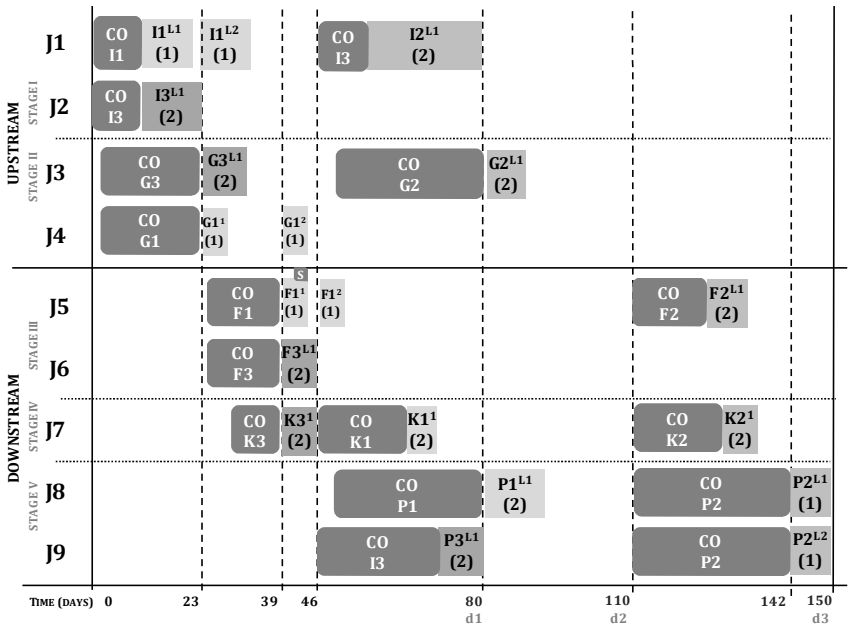

Figure 17 – Gantt chart for Example III with 8 event points, assuming no blending allowed of upstream stages intermediaries' lots (Solution: 106 rmu)

5 CONCLUSIONS

In this work a MILP formulation, based on a RTN continuous-time single time-grid formulation, was developed to solve the campaign planning/scheduling problems of biopharmaceutical processes. Acknowledging a fairly unexplored topic, the work was focused in addressing specific constraints of these biochemical processes not yet combined, which included the modelling of batch and/or continuous process steps, multiple intermediate deliveries, sequence dependent operations, storage of products regarding shelf-life limitations, and the track-control of the production lots for regulatory policies. The developed model was applied to three examples with different production layouts: the first example considered a mid-term planning problem representing the two main stages (upstream/downstream) of biopharmaceutical processes; the second example discussed additional model features onto a hybrid production process with three batch and continuous stages; and the third example extended the production layout considering the five main processing steps. Based on different industrial data sets and demand profiles, the model was able to solve the optimal schedule for each problem, providing the sequencing and allocation of the different processing units, the track record of campaign-lot quantities for each intermediate/product, the sequence-dependent changeover requirements and storage allocations. The results of the first example were compared with a discrete-time model, originally presented by Lakhdar et al. (2005), and discussed the advantages of the proposed continuous-time formulation in the duration/extent of scheduled campaign-tasks in order to fulfil the production demand.

As main conclusion, this work resumes a generic formulation to address the main campaign planning/scheduling challenges of biopharmaceutical processes. The RTN continuous time model was proven to be effective to solve the proposed industrial problems, particularly sensitive to changes in the tasks duration. Further research work will address alternative time-grid formulations to enhance computational performance into the complexity of real biopharmaceutical production processes, understanding the diverse model approaches and scalability. Some modelling aspects to overcome in future works are associated with the robustness of the storage features between batch and continuous tasks, the related control of shelf-life time constrains of stored materials, and the integration of operational parameters uncertainty to replicate real process variability.

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NOTATION

Indices	
d	delivery dates
i, i'	task
l	lot
r	resource (process unit, intermediate or final product)
t, t', t'', t'''	event point

Sets	
B	resources in which lots are allowed to be blended
D	delivery dates
D_r	delivery dates associated with resource *r*
E	processing equipment
E_{st}	subset of equipment related to storage
I	process tasks
I_r	tasks that require resource *r*
I_b	batch tasks
I_c	continuous tasks
I_{st}	storage tasks
I_{zw}	tasks subject to zero-wait policies
I_{mr}	tasks that must exceed a certain minimum rate
I^c_{rBC}	subset of continuous tasks that consumes the intermediate material *r* produced by a batch task
$I^B_{st}, I^C_{st}, I^{INT\_C}_{st}$	subset of storage tasks related to intermediates and final products produced by batch and continuous tasks
I^{st}_r	storage tasks associated with material resource *r*
L	lots
L_r	lots associated with resource *r*
L_i	lots associated with task *i*
L^r_B	lots of resource $r \in B$ that are able to be blended
M	material resources
M_{st}	subset of material resources able to be stored
P	subset of final products
R	process resources
RM	subset of raw material resources
T	event points

Parameters

α_i	constant term in the processing time of task *I*
β_i	proportional term to the extent variable in the processing time of task *I*
$\mu_{i,r}^{c}$	allocation coefficient for the binary extent of resource *r* (equipment unit) in task *I* relative to the start of the task
$\mu_{i,r}^{p}$	release coefficient for the binary extent of resource *r* (equipment unit) in task *I* relative to the end of the task
	processing time of task *k*
$\nu_{i,r}^{c}$	consumption coefficient for the continuous extent of *r* resource (intermediary or final product) in task *I* relative to the start of task
$\nu_{i,r}^{p}$	production coefficient for the continuous extent of resource *r* (intermediary or final product) in task *I* relative to the end of task
$\lambda_{i,r}$	coefficient for the rate of consumption of resource *r* by task *i*
c_r	cost of manufacturing resources *r*
c_r^u	backlog penalties cost
c_r^d	waste disposal cost
c_i^{st}	storage cost
$c_{i,i'}^{ch}$	sequence dependent {*I,i'*} changeover cost
υ_r	sales of resource r
H	time horizon
h_d	absolute time of demand point *d*
$\delta_{i,i'}$	time relative to task sequence changeover {*I,i'*}
$\sigma_{i,l}$.	lifetime of the processed products of the task *I* lot *l*
$Camp_{i,l}$.	minimum campaign length of the processing task *I* lot *l*
$\rho_i^{min}, \rho_i^{max}$	minimum and maximum allowable rate of task *i*
$Q_{r,d}^{mn}, Q_{r,l,d}^{max}$	minimum and maximum amount of resource *r* of one lot *l* at delivery *d*
$Q_{r,d}$	demand amount of each resource at delivery date *d*
$R_r^0, R_{r,l}^0$	resource availability in the beginning of the planning horizon
R_r^{max}	maximum resource availability of resource *r*
Δt	maximum number of consecutive events points allowed for batch tasks
$V_{i,l}^{min}$, $V_{i,l}^{max}$	minimum and maximum capacity of resource *r* (processing units) for task *I* of lot *l*

Variables

$C_{i,i',t}, C_{i,i,t}$	binary variable that assigns a sequence dependent changeover procedure to task *i* before time event *t*

$N_{i,l,t,t'}$	binary variable that assigns the task i of lot *l* to start at event point *t* and ended until point t'
$\xi_{i,l,t,t'}$	total amount of material processed by task *i* and lot *l* within the event interval [*t,t'*]
R_r^{init}	allocation of resource *r* (processing units)at the beginning of the scheduling horizon
$R_{r,l,t}$	resource availability *r* of lot *l* and time point *t*
$R_{r,l,t}^c, R_{r,l,t}^p$	amount consumed/produced of resource *r* of lot *l* and time point *t*
$S_{i,l,t,t'}$	binary variable that accounts when the product lifetime stored through task *i* lot *l* was extended within the interval [*t,t'*]
$x_{i,l,t,t'}$	accounts for the absolute storage time if storage task *i* lot *l* is active in the event interval [*t,t'*]
$W_{r,l,t}$	waste disposal amount when resource shelf-life is exceeded
$Y_{t,d}$	binary variable that assigns a specific event point *t* corresponds to a demand points *d*
$\Pi_{r,l,t}$	amount expedited at a corresponding due date
$\Pi_{r,l,t}^u$	unfulfilled demand of product *r* of lot *l*

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