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Optimal design of multiproduct batch plants considering duplication of units in series

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ABSTRACT

A generalized disjunctive programming (GDP) model for the optimal design of multiproduct batch plants is presented. This general model manages the duplication of units in series to perform a given operation in the process, which is an alternative that has not been considered in previous general approaches. Unlike duplication in parallel, duplication in series is only applicable to some operations which present trade-offs between duplication and other cost-impacting elements in the batch process. In order to use a fixed time and size factor model some assumptions had to be made in the operations that allow the duplication in series. To show the effectiveness of this approach, a plant that produces multiple recombinant proteins is presented and solved.

Keywords: Duplication in series; Multiproduct batch plants; Generalized disjunctive programming

1. Introduction

Throughout the last years, the design and the structural optimization of multiproduct batch plants have been extensively investigated. Nevertheless, the structural decision of duplicating units in series in a given operation has not been included in the general models for batch plant design published. In general, all works on this area had been based on a set of stages that was predetermined and fixed. Thus, the only structural decision that remains is the one related to unit duplication in parallel at each previously determined stage.

In this study, efforts are focused on multiproduct batch plants where several products with similar recipes are produced sequentially. Each product is manufactured at a time, in a sequence of operations. The plant operates in single product campaign (SPC) mode under a zero wait (ZW) policy. With the single product campaign approach, all the batches of a product are processed without overlapping with other products. In the ZW policy for scheduling a batch is transferred to the next unit as soon as the processing is completed in the current unit.

The batch plant design problem has the aim of determining the plant configuration, the equipment sizes and the number of equipment units in each stage that minimize the total investment cost (Voudouris and Grossmann, 1992, 1993; Ravemark and Rippin, 1998; Montagna et al., 2000). The habitual strategy for solving this problem is to consider constant values for size and time factors of each operation, information obtained from either laboratory or pilot plant. Following this approach, in this work a model using fixed size and time factors is developed in order to obtain a general systematic formulation.

Traditionally, in the batch process literature every processing task or operation of the production recipe of a product has been assigned to a processing unit named stage of the process. On the other hand, some works in bibliography have presented the option of merging tasks of the recipe in the same processing unit in the process (Birewar and Grossmann, 1990; Ravemark, 1995). Nevertheless, the option of dividing an operation or processing task of the recipe in several units connected in series has not been incorporated in general models for the design of multiproduct batch plants.

According to the literature analyzed, previous works regarding duplication in series in the design of batch plants were published by Corsano et al. (2004, 2006). These authors proposed to solve the design problem for the biomass/ethanol

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Nomenclature

Subscripts

h	units in series
i	product
m	units in parallel
p	operation

Superscripts

L	lower bound
U	upper bound

Parameters

C_i^{inoc}	inoculum cost per kg for producing product i
CCF	capital charge factor
CIN_i	total inoculum cost for producing product i in the time horizon H
H	time horizon
q_i	production requirement of product i
S_{ijph}	size factor of product i in operation p using configuration in series h
T^0_{ijph}	processing time of product i at stage j of operation p with h units in series
T^1_{ijph}	size factor of product i for semicontinuous unit in operation p with h units in series
T_{ijph}	cycle time of product i at stage j in operation p with h units in series
X	biomass concentration
α_p	cost coefficient for units in operation p
β_p	cost exponent for units in operation p

Binary variables

y_{jphm}	it is 1 if batch stage j in operation p with configuration h has m units in parallel out of phase
z_{ph}	it is 1 if configuration in series h is selected in operation p

Continuous variables

B_i	batch size of product i
b_i	logarithmic batch size of product i
C_{jp}	investment cost of stage j in operation p
CB_{jp}	investment cost of stage j in operation p
CR_p	investment cost of retentate unit in operation p
CS_p	investment cost of semicontinuous unit in operation p
n_i	number of batches of product i
R_p	size of semicontinuous unit in operation p
r_p	logarithmic size of semicontinuous unit in operation p
T_i	total time for producing product i
TL_i	limiting cycle time of product i
tl_i	logarithmic limiting cycle time of product i
u_{jp}	logarithmic size of a batch unit j in operation p
V_{jp}	size of a batch unit j in operation p
VR_p	size of retentate unit in operation p

fermentation stages including explicitly a superstructure that contemplates all the possible alternatives with regard the duplication of units in series or in parallel. Due to the elimination of binary variables, the resulting model is a nonlinear program (NLP). However, although this work represents the process with a high level of detail, is not a general model and is applied to the specific case of a fermentors network.

Previously published formulations of batch plant design generally involve mathematical programming methods, such as MILP (mixed-integer linear programming) and MINLP (mixed-integer nonlinear programming). In recent years, generalized disjunctive programming (GDP) has been employed as an alternative representation of mixed integer programming problems (Van den Heever and Grossmann, 1999; Lee and Grossmann, 2000; Vecchietti et al., 2003; Montagna et al., 2004; Sawaya and Grossmann, 2005). An attractive feature of GDP is that it allows a symbolic/quantitative representation of discrete and continuous optimization problems.

This work is motivated by the need of taking into account the duplication in series in general and systematic formulations of multiproduct batch plants design problems. A generalized disjunctive programming (GDP) model is proposed that is reformulated as a mixed-integer nonlinear program (MINLP) by the big-M relaxation. In this approach, every operation used to elaborate a product can be carried out in a single equipment unit or in several units working in series constituting, each of them, a stage in the process. In this way, the number of stages in the plant is a variable in the model. Moreover, each of these stages can have units with different sizes and be duplicated in parallel, each stage being independent from the remaining stages in the series.

It is important to mention that the trade-offs introduced in the process by the use of this new structural decision depend on the specific operation. Therefore, the effect is different from the traditional duplication in parallel out-of-phase that, independently of the operation considered, allows to reduce the limiting cycle time. Also, it is different from the duplication in parallel in-phase, whose effect for any stage is to process a bigger batch size and is generally used when the available upper bound for a piece of equipment is reached.

On the other hand, it is interesting to note that there are several processes whose operations present alternatives as regards the number of stages in series to be used. In a previous work (Moreno and Montagna, 2007), the vegetable extraction process was studied to include equipments in series to increase the efficiency of the operation of extraction, decreasing times and sizes of the equipment. Another particular example is the fermentation batch processes where, depending on the inoculum cost and the equipment cost, the optimal solution can vary the number of equipment units to be used and the way in which they should operate, i.e., in series and/or in parallel.

In order to evaluate the proposed approach, the process for the production of recombinant proteins is presented as example, where the operations of fermentation and homogenization present the structural option of duplication in series.

The remainder of this paper is organized as follows. In the next section, the definition of the problem under consideration is presented. In Section 3, the formulation of the model employing GDP is detailed while in Section 4 a summary of the formulation is given. A representative example corresponding to a plant of recombinant proteins is described. The applicability of the proposed approach is illustrated in Section 5 by a numerical example and a study of different structural alternatives. Finally, concluding remarks are made in Section 6.

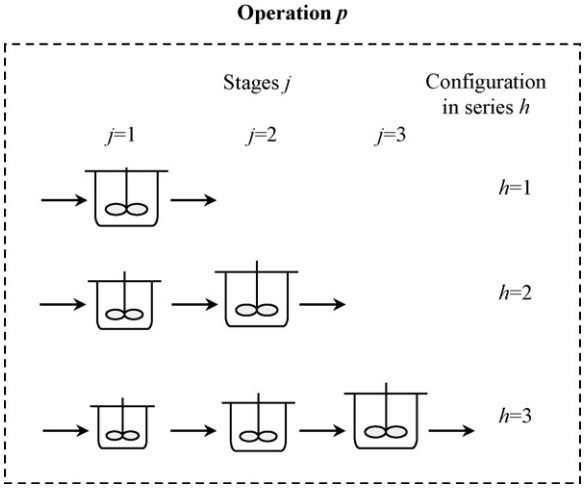

Fig. 1 – Configuration in series h for operation p.

2. Problem definition

The problem addressed in this work can be stated as follows. A multiproduct batch plant processes $i = 1, 2, \ldots, I$ products through $p = 1, 2, \ldots, P$ operations. For each operation p there may be different configurations h of units in series to perform it. Let H_p be the set of configurations in series available to perform operation p.

When a particular configuration h is selected for an operation p, this settles a sequence of stages j corresponding to each unit in series included in the operation. Let J_{ph} be the set of stages j included in the configuration h for the operation p. Fig. 1 illustrates the options for an operation, where three possible configurations in series are available, each of them composed of one, two, and three stages, respectively. It is convenient to emphasize that units belonging to a configuration in series can take equal or different sizes, which depends on the unit operation performed.

Furthermore, each stage j in operation p can be duplicated in parallel operating out-of-phase. Thus, each stage j may consist of m units working out-of-phase, with all the units of the same size. Let M_p be the maximum number of units that can be duplicated in each operation p. For each product i, there is a known production target q_i to be produced over a time horizon H.

3. Problem formulation

In order to get a better comprehension of the formulation, a batch plant for the production of proteins is taken as case of study. However, the presented model is general and can be applied to any multiproduct batch plant.

Consider a plant for producing multiple recombinant proteins (Montagna et al., 2000). Fig. 2 shows the flowsheet of the multiproduct batch plant. This process includes some operations which allow duplication in series of the units employed to perform them. All the products are synthesized during the operation of biomass fermentation, which can be performed in just one unit or in a series of units. In addition, the operation of homogenization can be performed with different configurations of units, as is described in more detail in later paragraphs. The products involved in the plant are human insulin, vaccine for hepatitis B, chymosin, and a cryophilic protease. A more detailed description of this process can be found in Montagna et al. (2000).

The problem formulation using general disjunctive programming (GDP) (Lee and Grossmann, 2000) is modeled through the following embedded disjunctions:

$$\bigvee_{h \in H_p} \left[\begin{array}{l} Z_{ph} \\ V_{jp} \geq S_{ijph}\, B_i \quad \forall i, j \in J_{ph} \\ VR_p \geq SR_{iph}\, B_i \quad \forall i \\ \bigvee_{m \in M_p} \left[\begin{array}{l} Y_{jphm} \\ TL_i \geq \dfrac{T^0_{ijph} + T^1_{ijph}\, B_i / R_p}{m} \quad \forall i \\ CB_{jp} = m\, \alpha_p\, V_{jp}^{\beta_p} \\ CS_p = N_h\, m\, \alpha s_p\, R_p^{\beta s_p} \\ CR_p = m\, \alpha r_p\, VR_p^{\beta r_p} \end{array} \right] \quad \forall j \in J_{ph} \end{array} \right] \tag{1}$$

Disjunctions have been defined for each operation p included in the process. Each disjunction has a term for each possible configuration h of units in series that can be used to perform operation p. A unique configuration of units in series must be chosen for each operation. Boolean variable Z_{ph} is true when configuration h is chosen for operation p and is false in the opposite case.

Once the configuration in series is selected, the duplication in parallel at each stage j in every operation p can be selected. Another set of disjunctions is posed for this purpose, embedded in the previous set where the configuration is selected. Boolean variable Y_{jphm} is true when m parallel units operating out-of-phase are used at the stage j in operation p with configuration in series h.

The design of batch plants is described through two kinds of equations included in disjunction (1). The first, known as size equations (Eq. (2)), enforces that the size of the units must permit the processing of the incoming batch at each stage of every operation.

$$V_{jp} \geq S_{ijph} B_i \tag{2}$$

The variable V_{jp} is the unit volume at stage j performing operation p and B_i is the batch size of product i. The parameter S_{ijph} is the size factor corresponding to product i at stage j in operation p using configuration h. This value is obtained from the recipe for product i and corresponds to the minimum capacity required in that piece of equipment, for producing one unit mass of product i.

Furthermore, the protein process involves some operations which are performed by a set of units that includes holding vessels and semicontinuous units, which process the material that is recirculated into the holding vessels. This occurs in the micro and ultrafilters operating between retentate and permeate vessels, and also in the homogenizer. In this case, Eq. (2) is applied not only to determine the unit size in general batch operations but to each of the items that compose aggregate units. So, in the case of microfilters, Eq. (2) applies to both the retentate and the permeate vessels. The parameter SR_{iph} is introduced to represent the size factor of the retentate vessel, while S_{iph} is left for the permeate vessel.

In order to obtain the fixed size factors for every stage of the series in an operation, it is necessary to compute them such that the batches entering and exiting the operation do not change with the configuration h. In other words, independently of the number of stages in series adopted, each operation delivers and receives the same batch size in all the

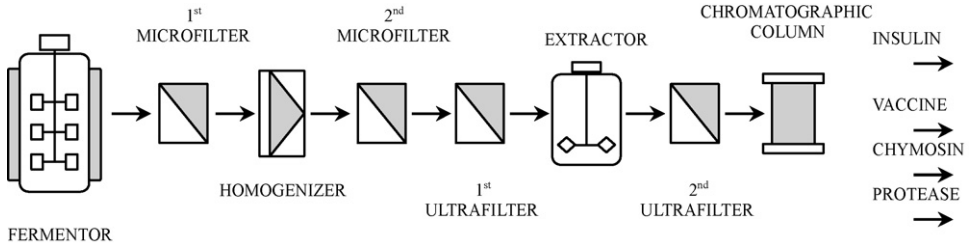

Fig. 2 – Flowsheet of the plant for the production of proteins.

options h considered, such that the size and time factors up and downstream of this stage remain unchanged.

The second equations for the design of batch plants are known as time equations. In this case, the operating time T_{ijph} for product i at stage j in operation p adopting a configuration h of units in series is given by:

$$T_{ijph} = T^0_{ijph} + T^1_{ijph} B_i \quad \forall i, j, p, h \tag{3}$$

This expression is composed of two terms: the first one, T^0_{ijph}, corresponds to a constant time, independent of the batch size to be processed; the second term is proportional to the batch size through a constant T^1_{ijph}. In the case of aggregated units, the processing time depends on the batch size and the capacity of the semicontinuous items as follows:

$$T_{ijhp} = T^0_{ijhp} + T^1_{ijhp} \frac{B_i}{R_p} \quad \forall i, j, p, h \tag{4}$$

where R_p refers to the size of the semicontinuous item that operates with the batch size B_i in operation p. The following equation determines the capacity of the semicontinuous units, as was proposed by Knopf et al. (1982)

$$R_p \geq \frac{D_{ip} B_i}{\theta_{ip}} \quad \forall i, p \tag{5}$$

where D_{ip} is the duty factor, i.e., the size necessary in operation p to process 1 kg of product i and θ_{ip} is the operating time that semicontinuous operation p needs to process a batch of product i.

Comparing Eq. (5) with the second term of Eq. (4) it can be concluded that it corresponds to the time of the semicontinuous unit and then T^1_{ijph} is the duty factor of that unit.

Multiproduct plants that work in overlapping mode operate cyclically producing consecutive batches of product i every cycle time, TL_i. It is given by the longest processing time among all the stages involved in the processing of product i. In order to reduce the cycle time of a product i, out-of-phase duplicated units at stage j can be introduced. This also decreases the idle time for up and downstream stages in case that stage j is the bottleneck for the production train, thus reducing the size of these stages.

Then, the constraint to determine the cycle time of product i in disjunction (1) is computed from the expression:

$$TL_i \geq \frac{T^0_{ijph} + T^1_{ijph} B_i / R_p}{m} \quad \forall i, j, p, h \tag{6}$$

Here a duplication of m out-of-phase parallel units at stage j of the configuration h in the operation p is considered.

The last constraints in the embedded disjunction in Eq. (1) represent the equipment costs of this alternative, which are a function of the capacity of the stages (Ravemark and Rippin, 1998). These costs include all components in operation p, i.e., batch units costs (CB_{jp}), semicontinuous units costs (CS_p), and retentate vessel costs (CR_p). Parameters α_p and β_p are cost coefficients used in the correlations for estimating the cost of unit volume V_{jp}. These coefficients are common for all stages that perform the same operation. Here, αs_p and βs_p are the cost coefficients and cost exponents for the semicontinuous items, used to compute their cost CS_p, and N_h is the number of semicontinuous units in series in option h. In this formulation and according to the solved examples, it is assumed that they all have the same size, although the model can be generalized allowing each semicontinuous unit to have a different capacity. In the operations of microfiltration the retentate vessel cost CR_p, is computed with the coefficients αr_p y βr_p. The cost of the permeate holding vessel CB_{jp} is obtained using the cost coefficient αp_p and the cost exponent βp_p.

The following condition establishes that the production targets of all products must be satisfied within the time horizon H.

$$\sum_i \frac{TL_i q_i}{B_i} \leq H \tag{7}$$

Thus, by this condition the summation of the processing times for producing I products is required not to be higher than the available time horizon.

The general objective of the model is to minimize the total cost of the plant ψ, satisfying the production targets q_i of I products considered in the time horizon. So, the objective function can be stated as follows:

$$\min \psi = \sum_p \sum_j CB_{jp} + \sum_p CS_p + \sum_p CR_p \tag{8}$$

In the previous equation, all stages j are taken into account according to the structural options (units in series and in parallel) selected for operation p. Similarly, semicontinuous and holding equipments included in those operations are also considered.

Considering that size and time factors must be determined and the special characteristics of the new structural option presented, the procedures to assess them are described in detail. Below, the fermentation and homogenization operations are selected taking into account both of them admit duplication in series.

3.1. *Fermentors in series*

In this process the first operation is biomass production, i.e., cell multiplication of genetically engineered *Saccharomyces cerevisiae* host, where the recombinant proteins are expressed during the cell growth. The option of duplicating in series the operation of fermentation is considered. Cell growth does not

start immediately after the inoculation (lag phase), and consequently it is recommended to employ an inoculum (3–10%) of a culture in exponential phase.

Before beginning each fermentation, the fermentor is fed with an appropriate substrate and then, sterilized. If there are more than one fermentor in series, the first biomass fermentor is inoculated with a broth containing biomass prepared in laboratory while the next ones are fed by the outlet stream of the preceding unit.

The initial biomass concentration in all fermentors in the series, $X^{i}_{j,fer}$, is the same. According to Pinto et al. (2001) maximum biomass concentration in this fermentation is $X_{i,max} = 55\,kg/m^3$ for all products and they considered inoculum that amounts to 5% of the fermentor capacity, so the initial biomass concentration is $X^{i}_{j,fer} = 2.75\,kg/m^3$.

A final concentration, $X^{f}_{j,fer}$, of 50 kg dry biomass/m^3 is assumed, where 40% of this biomass is proteins. Defining k_i as the ratio kg of product/kg of total proteins, it is estimated that $k_i = 0.05$, 0.1, 0.15, and 0.2 for insulin, vaccine, chymosin, and protease, respectively. Also, an overall yield of the process of 0.8 was estimated, i.e., 0.8 of the product obtained in the fermentation operation exits the chromatographic column.

Then, the size factor for the operation of fermentation for producing each product can be calculated as (Montagna et al., 2000)

$$S_{i,fer}(kg/m^3) = \frac{1}{50 \times 0.4 \times k_i \times 0.8} \tag{9}$$

As was previously mentioned, the concentration of the initial inoculum in every fermentor of the series must be kept constant, so it is possible to relate the initial concentration of the fermentor j to the final concentration of the unit that precedes it in the series $j-1$, with the following expression:

$$X^{f}_{j-1,fer} = \omega X^{i}_{j,fer} \tag{10}$$

Eq. (10) defines the dilution ratio between a fermentor and its predecessor in the series. In this case, for the data mentioned, it is a constant value equal to 18.18. This value is the relation between consecutive fermentor capacities in the series and allows estimating the size factors of units in series, related to the value in Eq. (9) that corresponds to the operation with a unique fermentor. Then,

$$\omega = \frac{S_{j,fer}}{S_{j-1,fer}} \tag{11}$$

Since the final concentrations are the same in all the equipments in the series, the same relation can be posed for the volumes

$$\omega = \frac{V_{j,fer}}{V_{j-1,fer}} \tag{12}$$

In other words, the size of each fermentor in the series is about 18 times smaller than the size of the next fermentor while the last fermentor in the series has always the same size factor, independent from the number of fermentors.

Table 1 summarizes the size factors for the operation of fermentation for each product i in every configuration h considering up to 3 stages in series.

The description of the fermentation is completed by estimating the processing time for product i. For this operation it is assumed a cell growth described by a logistic equation (Pinto et al., 2001):

$$\frac{dX_{i,fer}}{dt} = \phi_i X_{i,fer}\left(1 - \frac{X_{i,fer}}{X_{i,max}}\right) \quad \forall i \tag{13}$$

Integrating Eq. (13) between the initial and the final biomass concentration in the fermentor and adding a time for discharging, sterilizing, and charging, the processing time for each stage j when producing product i in the operation of fermentation is $T_{ijph} = 24$ h. Since the final biomass concentration is the same in each fermentor in the series, the time is the same in all the stages j that belong to each configuration in series h.

On the other hand, the inoculum seeded in the first fermentor in the series has also a large impact on total costs, and is included in the objective function of the problem. Basically, this variable trade-offs the structural optimization to determine the number of fermentors connected in series: more units in series requires less inoculum in the first fermentor in the series since each fermentor is 18 times smaller than the immediately posterior one in the series. Additionally, in this formulation the duplication of units in parallel out of phase is also considered.

Therefore, there exists a trade-offs between the inoculum volume and the investment in the fermentation units. Considering this, in the disjunction for the operation of fermentation the following equation must be added:

$$CIN_i = C^{inoc}_i X_{i,1,fer} V_{1,fer} \frac{q_i}{\omega B_i} \quad \forall i \tag{14}$$

In the previous expression, C^{inoc}_i is the inoculum cost per kg and CIN_i is the total inoculum cost necessary in the planning horizon for product i in operation p = *fermentation* which is seeded in the first unit in the series $j = 1$.

According to this, the inoculum cost in the overall objective function must be included together with the investment cost for equipment. In this way, the economical function to be minimized is the total cost (CT) of the process over the time horizon considered.

$$\min CT = CCF\left(\sum_p \sum_j CB_{jp} + \sum_p CS_p + \sum_p CR_p\right) + \sum_i CIN_i \tag{15}$$

Here, the capital charge factor CCF is a parameter which adjusts the investment cost to the operation horizon. Its value considers an amortization time of 5 years and a maintenance annual cost of 12.5% of investment cost.

3.2. *Homogenizers in series*

When the target protein is intracellular, cell wall must be disrupted to liberate it. This disruption must be appropriate, not excessive, to avoid denaturalization of the already liberated protein, and the useless liberation of pollutant material.

In this plant, the operation of homogenization performs cell disruption to liberate intracellular proteins vaccine and protease. An important design variable to achieve satisfactory cell disruption is the number of passes (NP) through the homogenizer valve. Although the amount of disruption can be increased substantially by using multiple passes through the

Table 1 – Operation of fermentation. Size factors S_{ijh}.

Series h	S_{ijh} (m^3/kg)											
	Insulin			Vaccine			Chymosin			Protease		
	$j=1$	$j=2$	$j=3$	$j=1$	$j=2$	$j=3$	$j=1$	$j=2$	$j=3$	$j=1$	$j=2$	$j=3$
1	1.250	–	–	0.625	–	–	0.415	–	–	0.3125	–	–
2	0.069	1.250	–	0.034	0.625	–	0.023	0.415	–	0.0172	0.3125	–
3	0.004	0.069	1.250	0.002	0.034	0.625	0.001	0.023	0.415	0.0009	0.0172	0.3125

homogenizer, each additional pass reduces the size of the cell debris, making its subsequent separation more difficult.

Because of this and according to Montagna et al. (2000) three passes through the homogenizer are adopted for all products in this process. This value is used to compute the duty factor of the semicontinuous item. In this operation, R_p in Eq. (5) is the capacity in cubic meters of suspension per hour. The size factor of the holding vessel corresponds to the final volume of the retentate vessel in the first microfiltration.

In the homogenization there exists the possibility of choosing between two configurations of the equipments with different number of units in series and three passes which are illustrated in Fig. 3. The first one uses only one semicontinuous unit whereas the second one uses a train of three semicontinuous units.

The first configuration in Fig. 3 corresponds to a unique semicontinuous unit where the material held in the batch item is passed three times. For example, for production of cryophilic protease, it was estimated that the fermentor broth is concentrated 4 times up to 200 kg/m^3 at microfilter 1. Because the intracellular protease is fully retained at the microfilter, the yield is 1. Then, the size factor of the homogenizer vessel is 4 times smaller than in the operation of fermentation, i.e., $S = 0.08\ m^3$/kg protease.

Hence, for this case, the duty factor of the homogenizer, as three passes are adopted, is the vessel size factor $0.08\ m^3/kg \times 3$, i.e., $D = 0.24\ m^3$/kg protease.

On the other hand, the second option to effect the same operation consists in performing it through three semicontinuous units in series, each of them constituting a pass to carry out the cell disruption. Therefore, these units constitute a semicontinuous subtrain operating simultaneously.

For the latter case, it is necessary to place two storage tanks: one before and the other after the semicontinuous train. In this study, it is assumed that these storage tanks can contain the material coming from the previous operation. The cost of these storage tanks is negligible compared with the cost of the process equipment so they are not included in the investment cost. For this reason, both storage tanks are shown in dotted lines in Fig. 3. For the example, the size factor of each homogenizer in the series is directly $D = 0.08\ m^3$/kg protease.

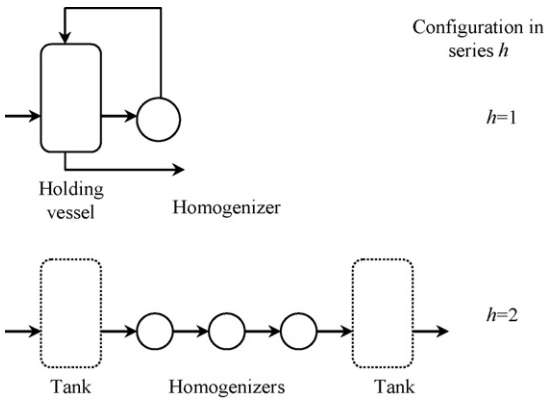

Fig. 3 – Configurations in series h for operation of homogenization.

In general, the configuration for this operation depends on the recipes of each product, i.e., if intracellular product A needs 3 passes and intracellular product B needs 5 passes, the option in series uses 5 homogenizers. Then, when product A is processed 2 units are bypassed. On the other hand, in the first option, with only one homogenizer the production is carried out re-circulating to the tank the number of passes corresponding to each product.

In order to include the options illustrated in Fig. 3, general disjunction (1) for the general process must be modified for the operation of homogenization since equations for each alternative are different. In this case, the parameter N_h takes the value 1 for $h = 1$ and the value 3 for $h = 2$.

In Table 2 the size factors are summarized for the semicontinuous unit in the operation of homogenization, for each product, in the options above presented.

4. Model summary and reformulation

In summary, the final model minimizes the total cost CT represented by Eq. (15) subject to disjunction (1) adding Eq. (14) in the disjunction for the operation of fermentation and constraint (7) over the time horizon plus bounds on the model variables. The constraints in the formulation present a posynomial form and therefore can be convexified through an exponential transformation as suggested by Grossmann and Sargent (1979). Therefore, the resulting model presents only one global optimum. In our implementation average values between the bounds of the variables were used as starting point.

According to Lee and Grossmann (2000), the GDP model allows a combination of algebraic and logical equations, which facilitates the representation of discrete decisions. Furthermore, for the GDP problem solution, two major methodologies are employed to transform disjunctions into a mixed-integer nonlinear program (MINLP): big-M and convex hull reformulations (Vecchietti et al., 2003). These transformations are required taking into account that the models must be formulated in a format compatible with the optimization program solvers. In this work, the big-M reformulation has been employed to solve the proposed model, which is detailed in Appendix.

5. Numerical example

The model was implemented and solved in the GAMS package (Brooke et al., 1998) on a Pentium (R) IV, 3.00 GHz. The code DICOPT was employed for solving the reformulated big-M MINLP problem.

Table 2 – Operation of Homogenization. Size factors T^1_{ijhp} [B_i (kg)].

Configuration in series h	T^1_{ijhp} (h)			
	Insulin	Vaccine	Chymosin	Protease
1	No	$0.465\,Cap^{-1}\,B_i$	No	$0.24\,Cap^{-1}\,B_i$
2	No	$0.155\,Cap^{-1}\,B_i$	No	$0.08\,Cap^{-1}\,B_i$

Table 3 – Product demands.

Product	Name	Production (kg/year)
1	Insulin	1500
2	Vaccine	1000
3	Chymosin	3000
4	Protease	6000

Table 4 – Size factors [*r*: retentate; *p*: permeate].

Operation	S_{ip} (m^3/kg)			
	Insulin	Vaccine	Chymosin	Protease
Microfiltration I	*r*: 1.25 *p*: 2.5	*r*: 0.625 *p*: No	*r*: 0.415 *p*: 0.830	*r*: 0.3125 *p*: No
Homogenization	No	0.155	No	0,08
Microfiltration II	No	*r*: 0.155 *p*: 0.31	No	*r*: 0.08 *p*: 0.16
Ultrafiltration I	2.50	0.31	0.830	0.16
Extraction	0.40	0.20	0.135	0.10
Ultrafiltration II	0.40	0.20	0.135	0.10
Chromatography	0.05	0.05	0.05	0.05

Table 5 – Time factors T^0_{ijhp}.

Operation	T^0_{ijhp} (h)			
	Insulin	Vaccine	Chymosin	Protease
Fermentation	24	24	24	24
Microfiltration I	1.75	1.25	1.75	1.25
Homogenization	No	1.25	No	1.25
Microfiltration II	No	1.75	No	1.75
Ultrafiltration I	1	1	1	1
Extraction	1.8	1.8	1.8	1.8
Ultrafiltration II	0.3	0.3	0.3	0.3
Chromatography	0.5	0.5	0.5	0.5

The example presented here was solved using the data summarized in Tables 1–7 and a planning horizon of 1 year (6000 h) was considered. Tables 4–6 present the size factors and processing times for each product in every operation in the production of recombinant proteins. The data corresponding to both fermentation and homogenization operations are presented in Sections 3.1 and 3.2 (see Tables 1 and 2).

In Table 7, α and β are cost coefficients according to Petrides et al. (1995). The inoculum cost C_i^{inoc} is assumed to be 100 \$/kg for all products i. The maximum number of stages assigned to the operation of fermentation is 3; therefore, there are 3 possible configurations of units in series for this operation ($H_1 = 3$). Each stage in the operations of this process can be duplicated up to 5 units in parallel. A lower bound of 0.1 m^3 is adopted for the unit sizes in the operation of fermentation.

The mathematical formulation involves 464 equations and 139 variables, 91 of which are binary variables. An optimal objective function value of \$498642.25 with a $CCF = 0.325$ was obtained after a CPU time of 508.79 s.

Fig. 4 illustrates the optimal structure of the plant. Here, two stages in series with four units in parallel in each one have been selected for the operation of fermentation. Also, three units in series have been selected in the operation of homogenization, while only one unit was adopted for the rest of the operations.

With two units in series in the operation of fermentation, the inoculum cost can be reduced significantly because it is proportional to the size of the first fermentor. Furthermore, the duplication of units in parallel out-of-phase in this operation occurs because the fermentation has the highest cycle time for all products. The limiting cycle time for this case was reduced from 24 to 6 h.

It is worth noting that the selection of the second configuration of units in series in the operation of homogenization allows reducing the unit sizes, i.e., three units with a size of 0.240 m^3/h each one instead of a unique unit with a size of 0.909 m^3/h if the first configuration was selected. It is important to note that the cost of semicontinuous units in the optimal solution for the operation of homogenization is \$4042.58. This value is larger than the cost of the first configuration, i.e., \$3659.92 (only one homogenizer). However, the cost of the associate batch unit (\$2324.54) must be added. Thus, the total cost for operation of homogenization with the first configuration is larger, i.e., \$5984.46. Because of this, in the optimal solution 3 homogenizers in series are selected.

Table 8 reports the optimal unit sizes obtained for each operation. It also indicates the number of out-of-phase duplicated units and the number of units operating in series.

5.1. *Study of different structural alternatives*

In order to analyze the sensitivity of the optimal plant design with the possible structural options, the posed model has been solved for different structural alternatives of the batch plant.

Table 6 – Time factors T^1_{ip} [B_i (kg)].

Operation	T^1_{ip} (h)			
	Insulin	Vaccine	Chymosin	Protease
Microfiltration I	$12.5\,A^{-1}\,B_i$	$2.5\,A^{-1}\,B_i$	$4.15\,A^{-1}\,B_i$	$1.25\,A^{-1}\,B_i$
Microfiltration II	No	$3.1\,A^{-1}\,B_i$	No	$1.6\,A^{-1}\,B_i$
Ultrafiltration I	$105\,A^{-1}\,B_i$	$5.5\,A^{-1}\,B_i$	$35\,A^{-1}\,B_i$	$3\,A^{-1}\,B_i$
Ultrafiltration II	$18\,A^{-1}\,B_i$	$8\,A^{-1}\,B_i$	$4.75\,A^{-1}\,B_i$	$3\,A^{-1}\,B_i$

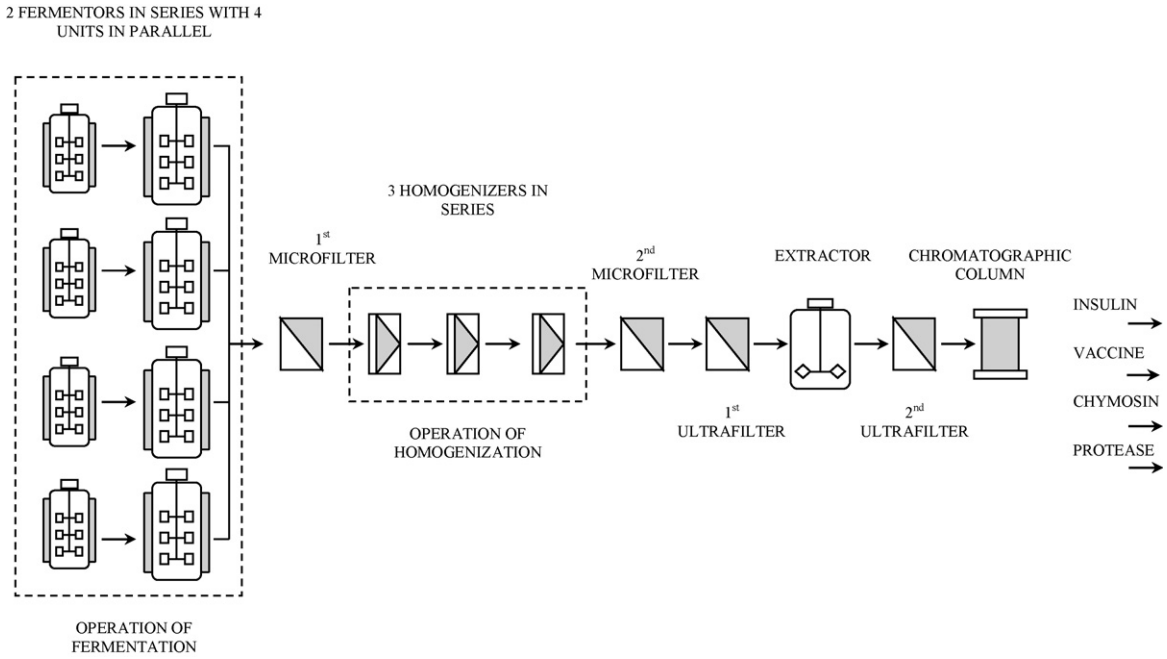

Fig. 4 – Optimal design for the recombinant protein plant.

Table 7 – Cost of equipment.

Unit	Size	Cost
Fermentor	V_j (m^3)	63400 $V^{0.6}$
Micro and ultrafilters	$V_{retentate}$ (m^3)	5750 $V_r^{0.6}$
	$V_{permeate}$ (m^3)	5750 $V_p^{0.6}$
	A_{filter} (m^2)	2900 $A^{0.85}$
Homogenizer	$V_{holding}$ (m^3)	5750 $V^{0.6}$
	Cap (m^3/h)	12100 $Cap^{0.75}$
Extractor	V_{extr} (m^3)	23100 $V^{0.65}$
Chromatography	V_{chrom} (m^3)	360000 $V^{0.995}$

5.1.1. *Case (a)*

In this case, the previous problem is considered without the option of adding units in parallel. Here, the optimal solution selected two stages in series for the fermentation and the homogenization is performed using 3 homogenizers in series, which corresponds to the second configuration mentioned in Section 3.2. Optimal unit sizes considering only duplication in series are summarized in Table 9. The value of the objective function for this problem is \$693056.93, a 39% larger than the previous one, and the limiting cycle time is 24 h. As the duplication in parallel was not allowed, the limiting time for all the products, determined by the operation of fermentation, could not be decreased. Therefore, others stages in the process present larger idle times which leads to employ larger units and thus higher costs for the plant.

The choice of two fermentation stages happens, as in the original solution, to reduce the amount of inoculum seeded in the first unit in the series.

Regarding the duplication in series in the homogenization, the choice of 3 semicontinuous units presents the same advantages that the optimal solution analyzed previously.

5.1.2. *Case (b)*

Previous published models do not consider the option of duplicating stages in series to perform an operation. In order to compare the approach proposed in this work with the traditional ones, the original problem was solved here without the option of duplicating in series. The optimal solution for this case duplicated out-of-phase the unique stage in the operation of fermentation. A detail of the optimal sizes and number of units in parallel is reported in Table 10. The resulting total annual cost in this case is \$538853.66, approximately an 8% higher than the value of the original optimal solution due to the bigger unit sizes that must be fed with inoculum in the operation of fermentation. Also, it can be seen in the operation of fermentation that 5 parallel units out-of-phase have been selected allowing the reduction of the cycle time to 4.8 h.

The number of units in parallel in the fermentor is larger than the obtained in the original solution, which reduces idle times in several operations.

It must be noted that the optimal plant structure found is the same as that obtained by Montagna et al. (2000) where the inoculum cost is not taken into account.

5.1.3. *Case (c)*

Finally, in this case no duplication was allowed, i.e., the operations of the plant can be duplicated neither in

Table 8 – Optimal solution for the design problem [*r*: retentate; *p*: permeate].

	Operation							
	1	2	3	4	5	6	7	8
V_{jp}	V_1: 0.309 V_2: 5.620	*p*: 11.240 *r*: 5.620	–	*p*: 2.877 *r*: 1.439	11.240	2.708	1.828	0.899
R_p	–	*A*: 13.224	*Cap*: 0.240	*A*: 6.770	*A*: 94.795	–	*A*: 14.198	–
m	4	1	1	1	1	1	1	1
h	2	1	3	1	1	1	1	1

Table 9 – Case a. Optimal solution for the problem without duplication in parallel [r: retentate; p: permeate].

	Operation							
	1	2	3	4	5	6	7	8
V_{jp}	V_1: 1.375 V_2: 25.00	p: 50.00 r: 25.00	–	p: 12.40 r: 6.20	50.00	12.00	8.100	3.00
R_p	–	A: 11.236	Cap: 0.258	A: 5.573	A: 91.304	–	A: 15.190	–
m	1	1	1	1	1	1	1	1
h	2	1	3	1	1	1	1	1

Table 10 – Case b. Optimal solution for the problem without duplication in series [r: retentate; p: permeate].

	Operation							
	1	2	3	4	5	6	7	8
V_{jp}	V_1: 4.496	p: 8.992 r: 11.392	1.151	p: 2.302 r: 2.825	8.992	2.167	1.463	0.719
R_p	–	A: 14.741	Cap: 0.973	A: 7.547	A: 99.784	–	A: 14.387	–
m	5	1	1	1	1	1	1	1
h	1	1	1	1	1	1	1	1

Table 11 – Case c. Optimal solution for the problem with no duplication [r: retentate; p: permeate].

	Operation							
	1	2	3	4	5	6	7	8
V_{jp}	V_1: 25.00	p: 50.00 r: 25.00	6.20	p: 12.40 r: 6.20	50.00	12.00	8.100	3.00
R_p	–	A: 11.236	Cap: 0.818	A: 5.573	A: 91.304	–	A: 15.190	–
m	1	1	1	1	1	1	1	1
h	1	1	1	1	1	1	1	1

Table 12 – Summary of costs associated with each case solved.

Description	Optimal value			
	Original problem	Case (a)	Case (b)	Case (c)
Inoculum cost	4676.07	5200.26	85011.00	94540.70
Cost of fermentors	272955.62	167091.46	253885.79	142146.65
Cost of other operations	221010.56	520765.21	199956.87	525456.00
Investment cost	493966.18	687856.67	453842.66	667602.65
CTA ($)	498642.25	693056.93	538853.66	762143.37

series nor in parallel. The unit sizes in the optimal solution are shown in Table 11. The total annualized cost is $762143.37 approximately a 53% higher than the original one.

Comparing Table 9 with Table 11, it can be concluded that all the equipment sizes are equal except for the fermentation and homogenization operations. First of all, the difference in costs occurs because the large amount of inoculum employed in this case since there is only one fermentor with a big size which has to be fed.

Table 12 presents a detail of inoculum total cost for producing all products for each studied case. In addition, it shows the investment cost, separating the cost of operation of fermentation from the other operations in the plant. The total investment cost and the annual cost obtained in the solution of each solved case are included in this table.

Comparing the results obtained, it can be clearly concluded that the approach proposed considering the new structural option of duplicating stages in series in the operations, besides the traditional option of duplicating units in parallel out-of-phase, allows to obtain a plant design with a considerably lower total cost.

It is necessary to highlight that in case (a) the inoculum cost is slightly larger than the optimal solution (first column), since the size of first fermentor in the series is bigger. Moreover, the total annual cost of the plant is a 39% larger than the original problem. Although the fermentor cost is lower, the equipment cost in other operations presents larger values because of their bigger sizes (see Table 9). As was mentioned

Table 13 – Fermentation—hypothetical study case.

Series h	T^0_{ijh1} (h)		
	j = 1	j = 2	j = 3
1	24	–	–
2	15	24	–
3	8	15	24

Table 14 – Hypothetical case. Optimal solution.

Stage j	Fermentation	
	Unit size (m^3)	Units in parallel
1	0.309	3
2	5.620	4

Table 15 – Optimal solutions for different inoculum costs.

Inoculum cost ($/kg)	Stages in series	Units in parallel	Unit sizes (m^3)	Inoculum total cost ($)	Cost of fermentors ($)	Total annual cost ($)
10	1	5	V_1: 4.496	8501.10	232206.51	460501.52
100	2	4	V_1: 0.309 V_2: 5.620	4676.07	272955.62	498642.25
1000	3	4	V_1: 0.100 V_2: 0.309 V_3: 5.620	2572.10	293658.59	529795.66

above, the prohibition of duplicating units in parallel for this case, does not allow the reduction of both idle times and unit sizes in the stages of the process.

In case (b), the inoculum cost is considerably larger than in the first two solved cases since there is only one fermentor with bigger size. The fermentor in case (c) is, actually, larger than in the other three previous cases because there is only one unit with bigger size in the operation of fermentation increasing the amount of inoculum seeded and thus, its cost is higher. Evidently, the selection of bigger sizes in all the units in case (c) occurs because both duplication options are not allowed.

Finally, for illustrating the capacity of the proposed approach in duplicating in series each stage independently, a hypothetical study case is posed, in which the times of each stage in the operation of fermentation are shown in Table 13, equal for all the products.

The optimal solution corresponds to a total annual cost of $488454.98. Table 14 presents the optimal configuration in the operation of fermentation. Other operations in the plant maintain the same configuration as in the original solution (see Table 8). Note that in stage 2, there are 4 units in parallel out-of-phase resulting in a limiting cycle time of 6 h. Moreover, it can be seen that in stages 1 the number units in parallel is 3. Thus, the approach proposed in this work allows different duplications in parallel for each stage in the series of the operation.

5.2. *Analysis of sensitivity of the results*

In this section, the dependence of the optimal solutions obtained with the process input data is analyzed.

The influence of the inoculum cost in the optimal plant configuration is analyzed. If the inoculum cost is small, the optimal solution tends to use a smaller number of units in series since the exponent 0.6 for the equipments cost penalizes the increase in the number of units due to economy of scale. On the other hand, if the inoculum cost increases, the ideal solution tends to use more units in series, with the unit size in the first stage as small as possible reducing the amount of inoculum to be feed. Then, the product (the final biomass) of each fermentor is the inoculum of the next unit in the series. Table 15 shows the unit sizes and configuration, with the total annual cost for different inoculum costs.

As can be seen in Table 15, in the first case the number of units in parallel selected is 5. Thus, the limiting cycle time given by the operation of fermentation is 4.8 h. In the last two cases, the number of units in parallel is 4 determining a limiting cycle time of 6 h.

However, in the last case the optimal configuration corresponds to 3 stages in series where the first fermentor in the series is in the lower bound. This leads to a considerable decrease in the inoculum total cost. It should be noted that this new first stage in the operation of fermentation (unit sizes of 0.1 m^3) would be actually carried out in the plant laboratory since the unit sizes correspond to a laboratory scale. Moreover, it should be noted that the first units of 0.1 m^3 (the lower bound) in the series are only using 0.017 m^3, due to the imposed relation of dilution between stages. Despite the subutilization of these units, it is convenient to incorporate them since it leads to an important decrease in the inoculum cost as can be observed in Table 15.

Summarizing, it is important considering the duplication of units in series because it poses alternatives and trade-offs with other cost-impacting elements of the model, which have not been analyzed in previous works.

6. Conclusions

In this paper, a general optimization model for the design of multiproduct batch plants using general disjunctive programming (GDP) has been developed. This model adds the duplication of stages in series as a new structural decision to perform a given operation of the process. Also, the traditional decision of duplicating units in parallel working out of phase is considered. Regarding the decision of duplicating units in series, the model presented allows that unit sizes in every stage of the series take different values. Moreover, it allows independent duplication of units in parallel in every stage of the series.

The GDP formulation of this problem allows a more compact representation and a better visualization of the proposed discrete decisions. This disjunctive problem was reformulated into a MINLP model by means of the big-M relaxation for its resolution. The optimization criterion consists in minimizing the total cost of the plant and, as a final convex formulation problem is obtained, the global optimality of the solution is guaranteed.

A biotechnological batch plant that elaborates recombinant proteins was presented as example to assess the proposed model. A particular feature of this process is the use of aggregated units in some operations, where semicontinuous units operate on the material contained in batch units. This particular characteristic of this process required to adapt the general disjunctive model. Furthermore, different configurations in series for the operations of fermentation and homogenization were described. The cost of the amount of inoculum added to the first fermentor in the series was also taken into account in the total costs.

Numerical results were obtained for a plant that produces four recombinant proteins in eight operations. The optimal solution resorts to the duplication of stages in series in the fermentation and homogenization operations. A trade-off exists between the number of stages in series in the fermentation, and the inoculum cost that is fed in the first of them.

Diverse structural alternatives were studied analyzing the impact of the duplication in series on the costs. It is possible to conclude that the duplication in series is an important structural option in multiproduct batch plants and that there are significant trade-offs with other decision variables on the plant, e.g., the number of units in parallel and the inoculum cost. All these elements must be considered simultaneously to study their effect on the total cost to be minimized.

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Appendix A. Big-M reformulation of the model

In order to obtain the big-M reformulation, the GDP model presented in Section 3 is reformulated as an MINLP model by transforming the disjunctive constraints into big-M constraints and replacing Boolean variables by binary variables (Vecchietti et al., 2003). First, taking into account the formulation presents a posynomial form, logarithmic variable transformations are introduced in order to convexify the model as suggested by Grossmann and Sargent (1979) and Ravemark and Rippin (1998):

$$u_{jp} = \ln\ V_{jp} \quad \forall j, p \tag{A.1}$$

$$b_i = \ln B_i \quad \forall i \tag{A.2}$$

$$tl_i = \ln TL_i \quad \forall i \tag{A.3}$$

$$r_p = \ln R_p \quad \forall p \tag{A.4}$$

$$ur_p = \ln VR_p \quad \forall p \tag{A.5}$$

Thus, after this logarithmic transformation of variables, the constraints presented in disjunction (1) can be transformed into the following MINLP problem:

$$\sum_h z_{ph} = 1 \quad \forall p \tag{A.6}$$

$$u_{jp} \geq \ln(S_{ijph}) + b_i - BM1_{jp}\,(1 - z_{ph}) \quad \forall i, p, h \in H_p, j \in J_{ph} \tag{A.7}$$

$$ur_p \geq \ln(S_{iph}) + b_i - BM2_p\,(1 - z_{ph}) \quad \forall i, p, h \in H_p \tag{A.8}$$

$$\sum_m y_{jphm} = z_{ph} \quad \forall p, h \in H_p, j \in J_{ph} \tag{A.9}$$

$$1 \geq \frac{T^0_{ijph}\exp(-tl_i) + T^1_{ijph}\exp(b_i - r_p - tl_i)}{m} - BM3_i\,(1 - y_{jphm})$$
$$\forall i, p, h \in H_p, j \in J_{ph}, m \in M_p \tag{A.10}$$

$$CB_{jp} \geq m\,\alpha_p\,\exp(\beta_p\,u_{jp}) - BM4_{jp}\,(1 - y_{jphm})$$
$$\forall p, h \in H_p, j \in J_{ph}, m \in M_p \tag{A.11}$$

$$CS_p \geq N_h m \alpha s_p \exp(\beta s_p r_p) - BM5_p(1 - y_{jphm})$$
$$\forall p, h \in H_p, j \in J_{ph}, m \in M_p \tag{A.12}$$

$$CR_p \geq m\alpha r_p \exp(\beta r_p ur_p) - BM6_p(1 - y_{jphm})$$
$$\forall p, h \in H_p, j \in J_{ph}, m \in M_p \tag{A.13}$$

$$CIN_i \geq mC^{inoc}_i X_{i,1,fer} \exp(u_{1,fer} - b_i)\frac{q_i}{\omega} - BM7_i(1 - y_{1,fer,h,m})$$
$$\forall i, m \in M_p, h \in H_p \tag{A.14}$$

A big-M constraint as Eq. (A.7) is satisfied if variable $z_{ph} = 1$. Otherwise, if z_{ph} is zero the corresponding constraint becomes redundant, taking into account that $BM1_{jp}$ is scalar large enough. Similar interpretations can be made for big-M constraints (A.8)–(A.14). The tightest values for the big-M scalars are used in above constraints in order to assure a good performance. They are calculated by the following expressions:

$$BM1_{jp} = u^U_{jp} \quad \forall j, p \tag{A.15}$$

$$BM2_i = ur^U_p \quad \forall i \tag{A.16}$$

$$BM3_i = \max_p(T^0_{ip} + T^1_{ip}\ \exp(b^U_i - r^L_p)) \quad \forall i \tag{A.17}$$

$$BM4_{jp} = M_p\alpha_p \exp(\beta_p\,u^U_{jp}) \quad \forall j, p \tag{A.18}$$

$$BM5_p = N_2 M_p \alpha s_p \exp(\beta s_p r^U_p) \quad \forall p \tag{A.19}$$

$$BM6_p = M_p \alpha r_p \exp(\beta r_p ur^U_p) \quad \forall p \tag{A.20}$$

$$BM7_i = M_{fer} C^{inoc}_i X_{i,1,fer} \exp(u^U_{1,fer} - b^L_i)\,\frac{q_i}{\omega} \quad \forall i \tag{A.21}$$

The big-M reformulation to the original problem consists of the objective function (15) subject to the convexified Eq. (7) and constraints (A.6)–(A.14).

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