Synthesis of Biotechnological Processes Using Generalized Disjunctive Programming

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This article presents a model for the synthesis of a biotechnological process in which a set of biotechnological products must be elaborated. For each of these products, there is a set of hosts that can be used for production. According to the host selected for each product, there is a different set of stages involved in the process. Furthermore, to carry out the task involved at a particular stage, there are different units that can be selected. Depending on the kind of equipment used, different performances can be obtained in terms of the stage yield, dimension required by the unit, processing time, etc. A generalized disjunctive programming model is formulated to solve this problem. This problem is transformed into an MINLP using either a big-M or convex hull reformulation. Both alternatives are solved, and their performances are evaluated.

Introduction

The biotechnological area is a field of intensive study because of the economic value of the products. Laboratories make great efforts to obtain products that meet various requirements. Once the product is developed in the laboratory, a production phase must be followed. For this purpose, several alternatives are evaluated to determine which one is the most viable. Up to the present, two different approaches have been used to solve this step: On one hand, there are models for process synthesis, and on the other hand, there are models regarding plant design. In the first case, the intention is to determine the kind of host to be used. In general, for the same product, the stages involved in the process are usually different according to the host being used. For each of these stages, there are different pieces of equipment that can carry out the required task. Depending on the equipment employed, the yield of the process is different. Therefore, the most appropriate option must be chosen for each stage.

In the plant design problem, the sequence of stages is already defined, and the process sequence is similar because different products usually share the stages. The most common case is the design of multiproduct batch plants. The problem goal is to determine unit sizes and configurations so as to meet the demands for all products in the given time horizon at the lowest possible cost. Each batch stage can be arranged in different ways, including in-phase or out-of-phase unit duplication, which allows for a reduction of the plant costs.

In general, the works in the literature dealing with similar problems address only partial portions of the whole problem. For example, Alvarez et al.[1] and Steffens et al.[2] emphasize the resolution of the synthesis problem. In the first work, the authors developed a mathematical mixed-integer linear program (MILP) to model the problem. In the other work, information on physical properties is taken into consideration to carry out the biotechnological process synthesis. As a result, the authors generate an ordered set of flow sheets that should be then analyzed from a design point of view with other tools. The authors address the purification section of a downstream process based on chromatographic stages. They also consider information on physicochemical data of a protein mixture.

Regarding multiproduct batch plant design, an extensive bibliography containing a general approach is available.[3−8] These works are characterized by a gradual advance, incorporating new alternatives to generate the models. There are also concrete applications of design of biotechnological processes.[9−11] These works analyze a recombinant protein production plant that produces four products, considering different levels of detail on the operation times and size factors.

In this work, we have integrated the two approaches by using a model that simultaneously considers synthesis and design aspects of the problem. In fact, previous works used partial views of a unique problem. The major drawback is developing the problem formulation is the difficulty of representing the whole problem because of the complexity in the number of discrete decisions to take into consideration.

A key factor in developing the model presented in this work is the use of generalized disjunctive programming.[12−14] As regards modeling, disjunctive programming facilitates the representation of complex situations involving multiple decision levels in a very simple way, yielding an easy-to-understand model.[15] For the problem solution, two methodologies are considered to transform disjunctions into a mixed-integer nonlinear program (MINLP): big-M and convex hull reformulations.

A real case example is solved involving four products, several hosts, and several batch stages, including fermentation and purification. The performances of both solution approaches are also evaluated.

Formulation of Discrete Decisions by Using Disjunctions

A generalized disjunctive programming model takes the following form[12]

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$$\min z = \sum_{k \in K} c_k + f(x)$$

$$\text{s.t.} \quad r(x) \leq 0$$

$$\bigvee_{j \in J_k} \begin{bmatrix} Y_{jk} \\ g_{jk}(x) \leq 0 \\ c_k = \gamma_{jk} \end{bmatrix}, \quad k \in K$$

$$\Omega(Y) = \text{true}$$

$$x \geq 0, \, c_k \geq 0, \, Y_{jk} \in \{\text{true, false}\} \tag{1}$$

In this model, $x \in R^n$ is the continuous variable vector, and Y_{jk} represents the Boolean variables. $c_k \in R^1$ represents the continuous variables, and γ_{jk} represents values that correspond to the evaluation of alternatives. $f\colon R^n \to R^1$ is the term of the objective function that depends on variables x, and $r\colon R^n \to R^q$ is a general set of constraints that do not depend on disjunctions. This general model assumes that $f(x)$ and $r(x)$ are convex functions.

A disjunction is composed of a set of terms linked by the logical OR operator. In each term of the disjunction, there is a Boolean variable Y_{jk}, a set of convex constraints $g_{jk}\colon R^n \to R^p$, and a cost variable c_k. If the Boolean variable Y_{jk} is true, then conditions $g_{jk}(x) \leq 0$ and $c_k = \gamma_{jk}$ must be met. Otherwise, if Y_{jk} is false, the corresponding constraints are ignored. It is assumed that each term of the disjunctions gives rise to a nonempty feasible region. Finally, $\Omega(Y) = \text{true}$ is a set of logical constraints generated by using the set of Boolean variables Y.

Model Formulation Using Generalized Disjunctive Programming

A model formulation is required to produce a set of P products. For each product i, there are different hosts h that can be used for its production. Let H_i be the set of hosts h that can be used to elaborate product i.

Depending on the host h being considered, a sequence of stages j that are to be included in the process is determined. Let J_h be the set of stages j included in the process that use host h.

For each stage j, there are different options d to carry out that task. Let D_j be the set of available options d for carrying out stage j.

The problem can be modeled using disjunctive programming by means of the following embedded disjunctions

$$\bigvee_{h \in H_i} \left[\bigvee_{d \in D_j} \begin{bmatrix} Y_{ih} \\ Z_{ihjd} \\ V_{jd} \geq \dfrac{S_{ijdh}B_i}{G_{jd}} \\ TL_i \geq \dfrac{T^0_{ijkh} + T^1_{ijdh}B_i}{M_{jd}} \end{bmatrix} \forall j \in J_h \right] \forall i \tag{2}$$

Disjunction 2 has been defined for each product. Each disjunction has a term for each possible host that can be used to produce product i. A unique host must be chosen for each product. Boolean variable Y_{ih} is true when host h is chosen for product i and is false in the opposite case.

Once the host is selected, its corresponding processing sequence is determined, but the equipment to be used

at each stage must be chosen. Another set of disjunctions is posed for this purpose, embedded in the previous set where the host is selected. Boolean variable Z_{ihjd} allows these alternatives to be considered; it is true when host h is used for product i and option d is employed to carry out stage j. At each term of the disjunction, two constraints are considered: the first is related to the unit volume and the second to the product cycle time.

At each stage, the available volume must be sufficient to process a batch according to the following constraint

$$V_{jd} \geq \frac{S_{ijdh}B_i}{G_{jd}} \tag{3}$$

V_{jd} is the unit volume at stage j using option d. S_{ijdh} is the size factor corresponding to product i at stage j using host h and option d. This value is obtained from the production recipe and corresponds to the volume needed in that piece of equipment to produce 1 kg of final product i. B_i is the batch of product i. Finally, G_{jd} is the number of in-phase parallel duplicated units for stage j, option d. As was pointed out in the Introduction, duplication of units is useful for the designer to attain the objective at a lower cost. In the case of in-phase duplicated units, each batch is shared among all units, which start and finish their processing at the same time.

For each product i, the cycle time is defined as the time that elapses between two successive batches of product i. It is given by the longest processing time among all processing stages of product i. For the purpose of reducing the cycle time for a particular product, it is possible to introduce out-of-phase duplicated units. The constraint to determine the cycle time of product i in disjunction 2 is given by

$$TL_i \geq \frac{T^0_{ijdh} + T^1_{ijdh}B_i}{M_{jd}} \tag{4}$$

where the numerator of the right-hand side corresponds to the operation time of product i at stage j using host h and option d. This time is composed of two terms: the first one, T^0_{ijdh}, corresponds to a constant time, independent of the batch size to be processed; the second term is proportional to the batch with a constant T^1_{ijdh}. Both parameters of this expression depend on the product, stage, equipment option, and host.

The objective function of the problem is to minimize the equipment cost

$$\min \text{cost} = \sum_j \sum_{\substack{d \\ d \in D_j}} \alpha_{jd} M_{jd} G_{jd} V_{jd}^{\beta_{jd}} \tag{5}$$

α_{jd} and β_{jd} are parameters used to evaluate the cost of unit volume V_{jd}. Simultaneous duplication of both in-phase and out-of-phase units is considered: there are out-of-phase groups of units M_{jd}, each one composed by G_{jd} in-phase units.

The following constraint ensures that, for each product i, a quantity Q_i must be produced in the available time horizon H

$$\sum_i \frac{Q_i TL_i}{B_i} \leq H \tag{6}$$

To solve the problem, the embedded disjunction 2 corresponding to stages with alternative units must be transformed into the form of a single disjunction as in the generalized disjunctive program proposed by Lee and Grossmann.[12,14] The following formulation results

$$
\bigvee_{d \in D_j}
\begin{bmatrix}
Z_{ihjd} \\
V_{jd} \geq \dfrac{S_{ijdh} B_i}{G_{jd}} \\
\mathrm{TL}_i \geq \dfrac{T^0_{ijdh} + T^1_{ijdh} B_i}{M_{jd}}
\end{bmatrix}
\quad \forall j \in J_h
$$

$$
Y_{ih} \Leftrightarrow \sum_{\substack{d \\ d \in D_j}} Z_{ihjd} \qquad \forall i,\, h \in H_i;\, j \in J_h \qquad (7)
$$

This formulation indicates that, when host h is used for product i, for each stage j included in the processing sequence of host h, an option d must be chosen among the alternatives available in that stage. Otherwise, if host h is not used for product i, neither stage j nor option d must be chosen.

It should be noted that this approach allows different options d to be chosen for the same stage j for different products. Another less general alternative could have been to demand that, at each stage, all products use the same option d.

The final model includes objective function 5 subject to conditions 2, 6, and 7, plus bound constraints on the model variables.

Regardless of the methodology being used to transform this generalized disjunctive programming model, the objective function is nonconvex, and the constraints present a posinomial form. The following transformations are then introduced to obtain a convex problem[3]

$$
v_{jd} = \ln V_{jd} \qquad (8)
$$

$$
b_i = \ln B_i \qquad (9)
$$

$$
tl_i = \ln \mathrm{TL}_i \qquad (10)
$$

$$
m_{jd} = \ln M_{jd} \qquad (11)
$$

$$
g_{jd} = \ln G_{jd} \qquad (12)
$$

Starting from the idea that variables M_{jd} and G_{jd} must take integer values, the following transformations are applied so that these variables can be handled as being continuous

$$
m_{jd} = \sum_k c_k ym_{jdk} \qquad \forall j,\, d \in D_j \qquad (13)
$$

$$
g_{jd} = \sum_k c_k yg_{jdk} \qquad \forall j,\, d \in D_j \qquad (14)
$$

$$
\sum_k ym_{jdk} = 1 \qquad \forall j,\, d \in D_j \qquad (15)
$$

$$
\sum_k yg_{jdk} = 1 \qquad \forall j,\, d \in D_j \qquad (16)
$$

where ym_{jdk} and yg_{jdk} are binary variables and $c_k = \ln k$. By using the mentioned elements, the objective

Table 1. Product Data

product	code name	production target
human insulin	INS	1500 kg/year
hepatitis B vaccine	HBV	1000 kg/year
tissue plasminogen activator	TPA	10 kg/year
superoxide dismutase	SOD	200 kg/year

Table 2. Hosts To Be Considered for Each Product

	host			
product	yeast extra	yeast intra	*E. coli*	CHO cells
INS	x		x	
HBV		x		x
TPA			x	x
SOD		x	x	

Table 3. Stages Considered for Each Host

		host			
		yeast			CHO
stage	operation	extra	intra	*E. coli*	cells
1	fermentation	x	x	x	x
2	solid−liquid separation	x	x	x	x
	2A. centrifugation				
	2B. microfiltration				
3	cell disruption		x	x	
	3A. homogenization				
	3B. bead milling				
4	solid−liquid separation			x	
	4A. centrifugation				
	4B. microfiltration				
5	IB solubilization			x	
6	diafiltration			x	
7	sulfonation			x	
8	refolding			x	
9	ultrafiltration			x	x
10	chromatography	x	x	x	x
11	ultrafiltration diafiltration	x	x	x	x
12	chromatography	x	x	x	x
13	ultrafiltration diafiltration	x	x	x	x
14	gel chromatography	x	x	x	x
15	sterile filtration	x	x	x	x

function and the corresponding constraints are modified as seen in the following section.

Example

Table 1 lists the products under consideration, together with their code names and annual demands. Four hosts are available for expressing these products: *Escherichia coli*, Chinese hamster ovary cells (CHO cells), and yeast (that, depending on the product, can be expressed as an extra- or intracellular protein). Table 2 indicates which alternative hosts can be used for each product processing.

According to the host selected, a sequence of processing stages is defined, as shown by Table 3. At stages 2−4, options options are available for performing the required tasks. In the case of stage 2 (cell harvesting operation), the options are centrifugation or membrane separation. These are also the same options for stage 4 (solid−liquid separation). At stage 3, cell rupture can be executed through homogenization or bead milling. A detailed description of the process can be found in Iribarren et al.[16]

Figure 1 shows the superstructure of the plant and the available options for each product. In particular, Figure 2 shows possible plant configurations for insulin, which are restricted to the use of yeast (extracellular) or *Escherichia coli* as hosts. It is noted that the stages to be used in each case are different. In addition to the
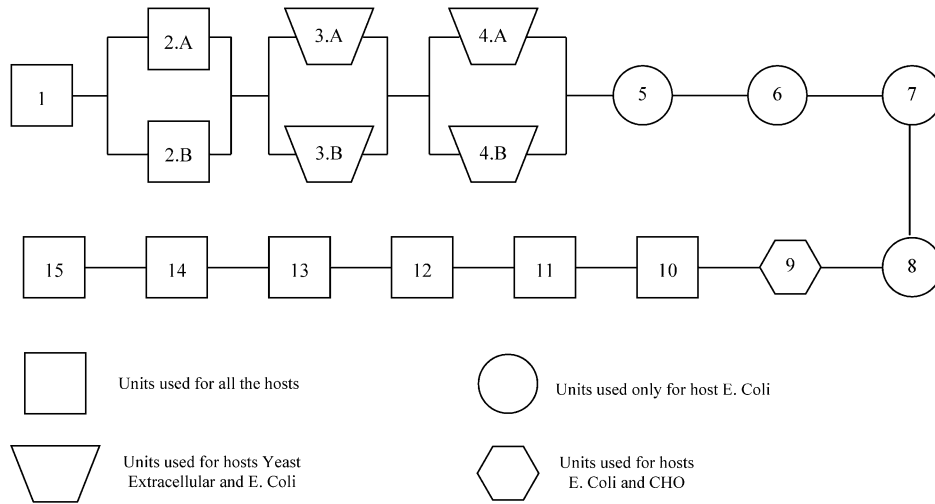
Figure 1. Stages used for each host.
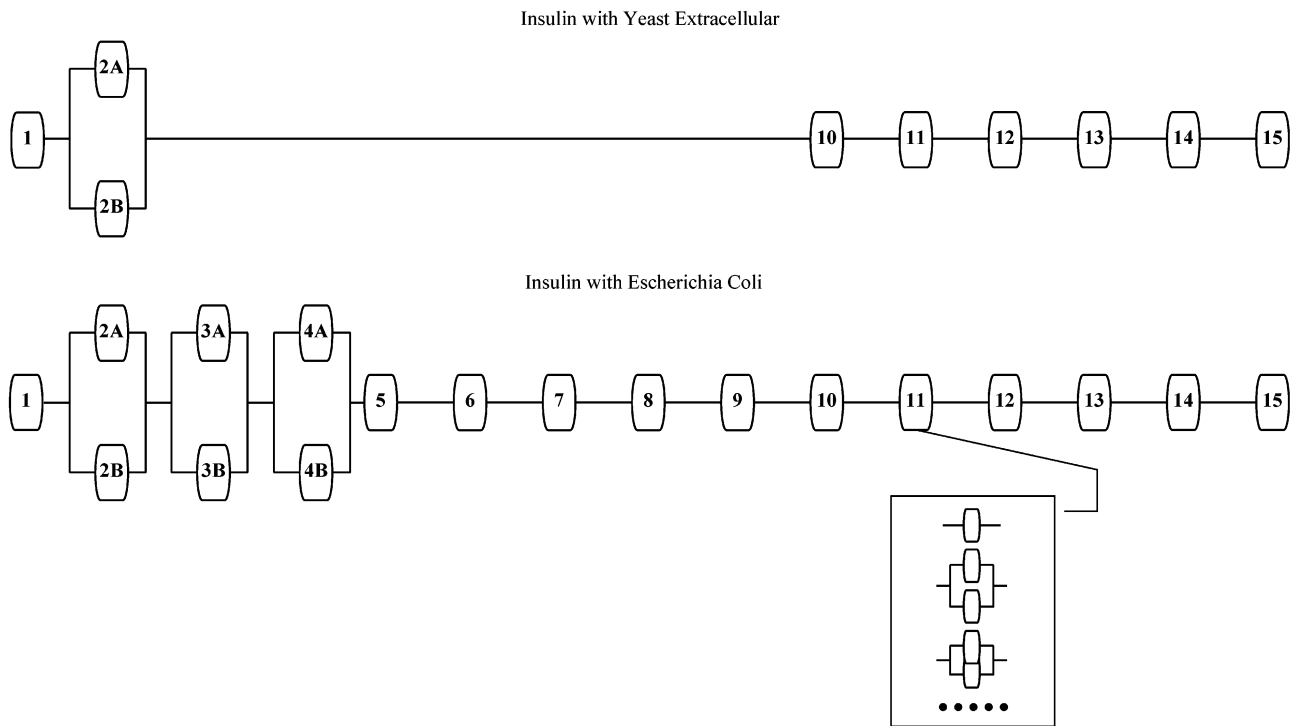
Figure 2. Options for insulin.

host selection and the processing options for some stages, the final process configuration is also be determined by in-phase and/or out-of-phase unit duplications.

The model applied to this particular problem presents some features as regards the previously presented basic model. Because of the characteristics of the included equipment, more sophisticated constraints are required for their modeling, which are described later.

The centrifuge, microfilter, homogeinizer, bead mill, diafiltration, ultrafiltration, and sterile filtration operations corresponding to stages 2−4, 6, 9, 11, 13 and 15 have been modeled by means of a set of units that includes holding vessels and semicontinuous units, which operate the material that is recirculated into the holding vessels.[9] The batch items are sized as previously described. The sizing equations for semicontinuous items are modeled according to a modification of a

similar expression proposed by Knopf et al.[4] allowing for in-phase unit duplications

$$G_{jd}R_{jd} \geq \frac{D_{ijdh}B_i}{\theta_{ijdh}} \qquad \forall i,\, h \in H_i;\, j \in J_h;\, d \in D_j \qquad (17)$$

where R_{jd} is the size of the semicontinuous unit at stage j using option d. D_{ijdh} is the duty factor, i.e., the size factor for semicontinuous items, for product i at stage j with option d using host h. θ_{ij} is the operating time that semicontinuous stage j, option d, needs to process a batch of product i using host h.[9]

The processes considered in this work have special semicontinuous units with an important economic impact on cost, including centrifuge, homogeinizer, ultrafilter, etc., but their operating time is the batch pro-

Table 4. Production Yields, η_{ijh}

		product/host							
	stage	INS/yeast	INS/*E. coli*	HBV/yeast	HBV/CHO	TPA/*E. coli*	TPA/CHO	SOD/yeast	SOD/*E. coli*
1	fermentation	1	1	1	1	1	1	1	1
2A	centrifugation	0.75	1	1	0.8	1	0.8	1	1
2B	microfiltration	0.85	1	1	0.9	1	0.9	1	1
3A	homogeinization	–	0.7	0.75	–	0.7	–	0.75	0.7
3B	bead milling	–	0.8	0.85	–	0.8	–	0.85	0.8
4A	centrifugation	–	1	0.8	–	1	–	0.8	1
4B	microfiltration	–	1	0.9	–	1	–	0.9	1
5	IB solubilization	–	0.7	–	–	0.7	–	–	0.7
6	ultrafiltration	–	01	–	–	1	–	–	1
7	sulfonation	–	0.9	–	–	0.9	–	–	0.6
8	refolding	–	0.6	–	–	0.6	–	–	0.6
9	ultrafiltration	–	1	–	1	1	1	–	1
10	chromatography	0.75	0.75	0.8	0.8	0.9	0.9	0.85	0.85
11	ultrafiltration	1	1	1	1	1	1	1	1
12	chromatography	0.9	0.9	0.85	0.85	0.9	0.9	0.85	0.85
13	ultrafiltration	1	1	1	1	1	1	1	1
14	gel chromatography	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
15	sterile filtration	1	1	1	1	1	1	1	1
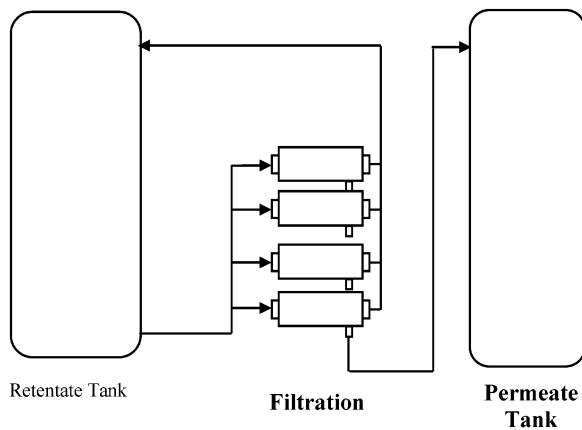
Figure 3. Special semicontinuous unit: microfilter.

cessing time of the respective stage. These types of aggregated units are shown in Figure 3 for the case of a microfilter. Their mathematical model was introduced by Salomone et al.[7] and has been modified for this problem to consider duplicated units operating in-phase. For the batch items, eq 2 is used. A time expression for the stage that depends on both the batch size and the size of the semicontinuous item is as follows

$$T_{ijdh} = T^0_{ijdh} + T^1_{ijdh}\frac{B_i}{G_{jd}R_{jd}} \qquad \forall i,\, h \in H_i;\, j \in J_h;\, d \in D_j \tag{18}$$

In expression 18, T^0_{ijdh} and T^1_{ijdh} are appropriate time factors that take into account contributions to the total cycle time of the stage. These possible contributions are (i) fixed amounts of time or (ii) times proportional to the batch size and inversely proportional to the size of the semicontinuous item.

Usually, using expression 18, the second term corresponds to the semicontinuous time θ_{ijdh}, and T^1_{ijdh} is given by the duty factor of the semicontinuous item D_{ijdh}. Expression 4 used to determine the cycle time is modified to represent the options described and becomes

$$\mathrm{TL}_i \geq \frac{T^0_{ijdh} + T^1_{ijdh}\dfrac{B_i}{G_{jd}R_{jd}}}{M_{jd}} \qquad \forall i,\, h \in H_i;\, j \in J_h;\, d \in D_j \tag{19}$$

Table 5. Cost Data (U.S. $) for All Stages

stage	cost function, equipment		
1		$63\,400\,V^{0.6}$ fermentor	
2A	$5750\,V^{0.6}$ feed tank	$28\,600\,R^{0.7}$ centrifuge	$5750\,V^{0.6}$ product tank
2B	$5750\,V^{0.6}$ retentate tank	$2900\,R^{0.85}$ microfilter	$5750\,V^{0.6}$ permeate tank
3A	$5750\,V^{0.6}$ holding tank	$12\,100\,R^{0.75}$ homogenizer	
3B	$5750\,V^{0.6}$ holding tank	$27\,630\,R^{0.5}$ bead mill	
4A	$5750\,V^{0.6}$ feed tank	$28\,600\,R^{0.7}$ centrifuge	$5750\,V^{0.6}$ product tank
4B	$5750\,V^{0.6}$ retentate tank	$2900\,R^{0.85}$ microfilter	$5750\,V^{0.6}$ permeate tank
5		$31\,000\,V^{0.5}$ solubilization reactor	
6	$5750\,V^{0.6}$ holding tank	$2900\,R^{0.85}$ diafilter	
7		$31\,000\,V^{0.5}$ sulfonator	
8		$31\,000\,V^{0.5}$ refolding reactor	
9	$5750\,V^{0.6}$ holding tank	$2900\,R^{0.85}$ ultrafilter	
10	$5750\,V^{0.6}$ holding tank	$310\,000\,A^{0.55}$ chromatographic column	$5750\,V^{0.6}$ product tank
11	$5750\,V^{0.6}$ holding tank	$2900\,R^{0.85}$ ultrafilter	
12	$5750\,V^{0.6}$ holding tank	$310\,000\,A^{0.55}$ chromatographic column	$5750\,V^{0.6}$ product tank
13	$5750\,V^{0.6}$ holding tank	$2900\,R^{0.85}$ ultrafilter	
14	$5750\,V^{0.6}$ holding tank	$310\,000\,A^{0.55}$ chromatographic column	$5750\,V^{0.6}$ product tank
15	$5750\,V^{0.6}$ feed tank	$2900\,R^{0.85}$ centrifuge	$5750\,V^{0.6}$ permeate tank

The objective function is also modified to take into account the different vessels included in each option. The expression for the semicontinuous items is similar to that for continuous units.

Tables 4–7 include data corresponding to this problem for each stage of the plant and, where appropriate, for each available option at each stage using a previous example.[16] Table 4 details the yield for each piece of equipment for all stages and all possible combination of products and hosts. Tables 5–7 correspond to the cost

Table 6. Size (S_{ijdh}) and Duty (D_{ijdh}) Factors for All Stages

stage, equipment	product/host							
	INS/yeast	INS/*E. coli*	HBV/yeast	HBV/CHO	TPA//*E. coli*	TPA/CHO	SOD/yeast	SOD/*E. coli*
1 fermentation	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.03/\prod_{j=2}^{15}\eta_{ijh}$	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$1/\prod_{j=2}^{15}\eta_{ijh}$	$10/\prod_{j=2}^{15}\eta_{ijh}$	$0.04/\prod_{j=2}^{15}\eta_{ijh}$	$0.05/\prod_{j=2}^{15}\eta_{ijh}$
2A centrifugation								
feed tank	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.03/\prod_{j=2}^{15}\eta_{ijh}$	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$1/\prod_{j=2}^{15}\eta_{ijh}$	$10/\prod_{j=2}^{15}\eta_{ijh}$	$0.04/\prod_{j=2}^{15}\eta_{ijh}$	$0.05/\prod_{j=2}^{15}\eta_{ijh}$
centrifuge D_{ih}	$0.0025/\prod_{j=2}^{15}\eta_{ijh}$	$0.15/\prod_{j=2}^{15}\eta_{ijh}$	$0.005/\prod_{j=2}^{15}\eta_{ijh}$	$0.0025/\prod_{j=2}^{15}\eta_{ijh}$	$5/\prod_{j=2}^{15}\eta_{ijh}$	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.002/\prod_{j=2}^{15}\eta_{ijh}$	$0.125/\prod_{j=2}^{15}\eta_{ijh}$
product tank	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.015/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$10/\prod_{j=2}^{15}\eta_{ijh}$	$0.01/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$
2B microfiltration								
retentate tank	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.03/\prod_{j=2}^{15}\eta_{ijh}$	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$1/\prod_{j=2}^{15}\eta_{ijh}$	$10/\prod_{j=2}^{15}\eta_{ijh}$	$0.04/\prod_{j=2}^{15}\eta_{ijh}$	$0.05/\prod_{j=2}^{15}\eta_{ijh}$
microfilter D_{ih}	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$0.12/\prod_{j=2}^{15}\eta_{ijh}$	$0.375/\prod_{j=2}^{15}\eta_{ijh}$	$2.2/\prod_{j=2}^{15}\eta_{ijh}$	$4/\prod_{j=2}^{15}\eta_{ijh}$	$44/\prod_{j=2}^{15}\eta_{ijh}$	$0.15/\prod_{j=2}^{15}\eta_{ijh}$	$0.2/\prod_{j=2}^{15}\eta_{ijh}$
permeate tank	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	no	no	$0.7/\prod_{j=2}^{15}\eta_{ijh}$	no	$14/\prod_{j=2}^{15}\eta_{ijh}$	no	no
3A homogenization								
holding tank	−	$0.015/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.01/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$
homogenizer	−	$0.045/\prod_{j=2}^{15}\eta_{ijh}$	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	−	$1.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.04/\prod_{j=2}^{15}\eta_{ijh}$	$0.075/\prod_{j=2}^{15}\eta_{ijh}$
3B bead milling								
holding tank	−	$0.015/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.01/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$
bead mill D_{ih}	−	$0.045/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$	−	$1.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.01/\prod_{j=2}^{15}\eta_{ijh}$	$0.075/\prod_{j=2}^{15}\eta_{ijh}$
4A centrifugation								
feed tank	−	$0.015/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.01/\prod_{j=2}^{15}\eta_{ijh}$	$0.025/\prod_{j=2}^{15}\eta_{ijh}$
centrifuge D_{ih}	−	$0.1875/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	−	$6.25/\prod_{j=2}^{15}\eta_{ijh}$	−	$0.2/\prod_{j=2}^{15}\eta_{ijh}$	$0.3125/\prod_{j=2}^{15}\eta_{ijh}$
product tank	−	no	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	−	no	−	$0.02/\prod_{j=2}^{15}\eta_{ijh}$	no
4B centrifugation								
retentate tank	$0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.03/\prod_{j=2}^{15}\eta_{ijh}$	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$1/\prod_{j=2}^{15}\eta_{ijh}$	$10/\prod_{j=2}^{15}\eta_{ijh}$	$0.04/\prod_{j=2}^{15}\eta_{ijh}$	$0.05/\prod_{j=2}^{15}\eta_{ijh}$
microfilter D_{ih}	$0.5/\prod_{j=2}^{15}\eta_{ijh}$	$0.12/\prod_{j=2}^{15}\eta_{ijh}$	$0.375/\prod_{j=2}^{15}\eta_{ijh}$	$2.2/\prod_{j=2}^{15}\eta_{ijh}$	$4/\prod_{j=2}^{15}\eta_{ijh}$	$44/\prod_{j=2}^{15}\eta_{ijh}$	$0.15/\prod_{j=2}^{15}\eta_{ijh}$	$0.2/\prod_{j=2}^{15}\eta_{ijh}$
permeate tank	$0.1/\prod_{j=2}^{15}\eta_{ijh}$	no	no	$0.7/\prod_{j=2}^{15}\eta_{ijh}$	no	$14/\prod_{j=2}^{15}\eta_{ijh}$	no	no
5 IB solubilization	−	$0.1/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$1/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$0.5/\prod_{j=5}^{15}\eta_{ijh}$
6 diafiltration								
holding tank	−	$0.01/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$1/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$0.5/\prod_{j=5}^{15}\eta_{ijh}$
diafilter D_{ih}	−	$7/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$70/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$35/\prod_{j=5}^{15}\eta_{ijh}$
7 sulfonation	−	$0.12/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$1.2/\prod_{j=5}^{15}\eta_{ijh}$	−	−	$0.6/\prod_{j=5}^{15}\eta_{ijh}$
8 refolding	−	$1/\prod_{j=8}^{15}\eta_{ijh}$	−	−	$20/\prod_{j=8}^{15}\eta_{ijh}$	−	−	$2/\prod_{j=8}^{15}\eta_{ijh}$
9 ultrafiltration								
holding tank	−	$1/\prod_{j=8}^{15}\eta_{ijh}$	−	from 2A $0.5/\prod_{j=3}^{15}\eta_{ijh}$ from 2B $0.7/\prod_{j=2}^{15}\eta_{ijh}$	$20/\prod_{j=8}^{15}\eta_{ijh}$	from 2A $10/\prod_{j=3}^{15}\eta_{ijh}$ from 2B $14/\prod_{j=2}^{15}\eta_{ijh}$	−	$2/\prod_{j=8}^{15}\eta_{ijh}$
ultrafilter D_{ih}	−	$50/\prod_{j=8}^{15}\eta_{ijh}$	−	from 2A $25/\prod_{j=3}^{15}\eta_{ijh}$ from 2B $35/\prod_{j=2}^{15}\eta_{ijh}$	$1000/\prod_{j=8}^{15}\eta_{ijh}$	from 2A $500/\prod_{j=3}^{15}\eta_{ijh}$ from 2B $700/\prod_{j=2}^{15}\eta_{ijh}$	−	$100/\prod_{j=8}^{15}\eta_{ijh}$
10 chromatography								
feed tank	from 2A $0.05/\prod_{j=3}^{15}\eta_{ijh}$ from 2B $0.1/\prod_{j=2}^{15}\eta_{ijh}$	$0.4/\prod_{j=10}^{15}\eta_{ijh}$	from 4A $0.02/\prod_{j=2}^{15}\eta_{ijh}$ from 4B $0.05/\prod_{j=2}^{15}\eta_{ijh}$	$0.4/\prod_{j=10}^{15}\eta_{ijh}$	$0.4/\prod_{j=10}^{15}\eta_{ijh}$	$0.4/\prod_{j=10}^{15}\eta_{ijh}$	from 4A $0.008/\prod_{j=3}^{15}\eta_{ijh}$ from 4B $0.02/\prod_{j=2}^{15}\eta_{ijh}$	$0.4/\prod_{j=10}^{15}\eta_{ijh}$
chromatographic column	$0.5/\prod_{j=10}^{15}\eta_{ijh}$	$0.5/\prod_{j=10}^{15}\eta_{ijh}$	$0.5/\prod_{j=10}^{15}\eta_{ijh}$	$0.8/\prod_{j=10}^{15}\eta_{ijh}$	$0.5/\prod_{j=10}^{15}\eta_{ijh}$	$0.8/\prod_{j=10}^{15}\eta_{ijh}$	$0.8/\prod_{j=10}^{15}\eta_{ijh}$	$0.8/\prod_{j=10}^{15}\eta_{ijh}$
product tank	$0.1/\prod_{j=11}^{15}\eta_{ijh}$	$0.1/\prod_{j=11}^{15}\eta_{ijh}$	$0.1/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	$0.1/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$
11 ultrafiltration								
holding tank	**0.1**$/\prod_{j=11}^{15}\eta_{ijh}$	**0.1**$/\prod_{j=11}^{15}\eta_{ijh}$	**0.1**$/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	**0.1**$/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$	$2/\prod_{j=11}^{15}\eta_{ijh}$
ultrafilter D_{ih}	$5/\prod_{j=11}^{15}\eta_{ijh}$	$5/\prod_{j=11}^{15}\eta_{ijh}$	$5/\prod_{j=11}^{15}\eta_{ijh}$	$100/\prod_{j=11}^{15}\eta_{ijh}$	$5/\prod_{j=11}^{15}\eta_{ijh}$	$100/\prod_{j=11}^{15}\eta_{ijh}$	$100/\prod_{j=11}^{15}\eta_{ijh}$	$100/\prod_{j=11}^{15}\eta_{ijh}$
12 chromatography								
feed tank	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$	$0.05/\prod_{j=12}^{15}\eta_{ijh}$
chromatographic column	$0.7/\prod_{j=12}^{15}\eta_{ijh}$	$0.7/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$	$0.8/\prod_{j=12}^{15}\eta_{ijh}$
product tank	$1/\prod_{j=13}^{15}\eta_{ijh}$	$1/\prod_{j=13}^{15}\eta_{ijh}$	**2**$/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$
13 ultrafiltration								
holding tank	$1/\prod_{j=13}^{15}\eta_{ijh}$	$1/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$	$2/\prod_{j=13}^{15}\eta_{ijh}$
ultrafilter D_{ih}	$50/\prod_{j=13}^{15}\eta_{ijh}$	$50/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$	$100/\prod_{j=13}^{15}\eta_{ijh}$
14 chromatography								
feed tank	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$	$0.05/\prod_{j=14}^{15}\eta_{ijh}$
chromatographic column	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$	$0.4/\prod_{j=14}^{15}\eta_{ijh}$
product tank	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$
15 centrifugation								
feed tank	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$
centrifuge D_{ih}	1	1	1	1	1	1	1	1
product tank	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$	$0.1/\prod_{j=15}^{15}\eta_{ijh}$

Table 7. Processing Times (T_{ijdh}) for All Stages

stage	product/host							
	INS/yeast	INS/E. coli	HBV/yeast	HBV/CHO	TPA/E. coli	TPA/CHO	SOD/yeast	SOD/E. coli
1	24	24	24	168	24	168	24	24
5	—	8	—	—	12	—	—	10
7	—	12	—	—	18	—	—	15
8	—	8	—	—	12	—	—	10
10	$3.5 + \dfrac{0.6B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$3.5 + \dfrac{0.6B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$3.5 + \dfrac{0.6B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$3.5 + \dfrac{0.35B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=10}^{15}\eta_{ijh}}$
12	$8 + \dfrac{0.5B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$8 + \dfrac{0.5B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$	$15 + \dfrac{0.35B_i}{G_jA_j\prod_{j=12}^{15}\eta_{ijh}}$
14	5	5	5	5	5	5	5	5

Table 8. Bounds on Equipment Sizes

unit	lower bound	upper bound
fermentor (V)	0.2 m³	100 m³
microfilter (R)	0.1 m³	50 m³
homogeinizer (R)	0.1 m³/h	20 m³/h
bead mill (R)	0.05 m³/h	10 m³/h
centrifuge (R)	0.1 kW	20 kW
reactors (V)	0.2 m³	100 m³
chromatograph (A)	0.0001 m²	0.75 m²
tanks (V)	0.2 m³	100 m³

data, size factors, and processing times, respectively, for all stages in the problem. Stages 1, 5, 7, and 8 are standard batch stages, for which the equations presented in the model description are used. The remaining stages are units that include at least one batch item and another item that is semicontinuous. In this case, eq 3 is used for batch items, whereas eq 19 is used for semicontinuous items considering the transformation of the operation time using eq 17. In the case of stages 10, 12, and 14, which correspond to chromatography, the variable corresponding to the semicontinuous item is called A_{jd}, and this variable is sized according to the unit area and not to its production rate. Table 8 lists lower and upper bounds for the units involved in the plant.

Problem Solution

Two approaches were used to solve this problem: big-M and convex hull reformulations. The performances of the two approaches are compared.

Big-M Formulation. A general disjunction for the linear case can be expressed as follows

$$F = \underset{i \in D}{\vee} [a_i^T x \le b_i] \qquad x \in R^n \qquad (20)$$

The big-M relaxation for the set F is the following[13]

$$a_i^T x \le b_i + M_i(1 - y_i) \qquad (21)$$

$$\sum_i y_i = 1 \qquad (22)$$

where y_i is a binary variable and M_i is a scalar big enough that, if $y_i = 0$, inequality 21 becomes redundant and, if $y_i = 1$, inequality 21 must be satisfied. The tightest value that for the M_i scalar can be determined by the following expression

$$M_i = \max (a_i^T x - b_i, \quad x^{lo} \le x \le x^{up}) \qquad (23)$$

Note that, to determine the best value for M_i, bounds for the continuous variables must be provided.

For the nonlinear case, the following general disjunction can be posed

$$F = \underset{i \in D}{\vee} [h_i(x) \le 0] \qquad x \in R^n \qquad (24)$$

where $h_i(x) \le 0$ is assumed to be convex and continuous. The big-M formulation of eq 24 is

$$h_i(x) \le M_i(1 - y_i) \qquad (25)$$

plus eq 22. The tightest value for M_i in this case can be calculated as follows

$$M_i = \max(h_i(x), \quad x^{lo} \le x \le x^{up}) \qquad (26)$$

Big-M Reformulation Model for the Biotechnological Process

The big-M reformulation allows us to simplify the mathematical model by taking advantage of knowledge about the problem structure to reduce the number of equations and constraints. For example, in the big-M problem reformulation, the batch stages that do not present an alternative unit configuration are considered constraints independent of discrete choices. The objective function of the posed problem using the transformation posed in expressions 8, 11, and 12 is

$$\min \text{cost} = \sum_j \sum_{\substack{d \\ d \in D_j}} \alpha_{jd} \exp(m_{jd} + g_{jd} + \beta_{jd} v_{jd}) \qquad (27)$$

For the purpose of simplifying this presentation, the objective function does not include references to the stages that include several batch items and semicontinuous items, which should be taken into account in that expression.

In the rest of this article, two types of stages will be distinguished: those that have alternatives in the units that operate the stage (set Alt), i.e., stages 2−4, and those that do not have options, i.e., the remaining stages. The purpose of distinguishing these two sets is to limit the number of binary variables to be used in the model. For those stages in which there are no alternative pieces of equipment to carry out the task, only the host selection is needed, and therefore, binary variables y_{ih} are used. For the case of stages presenting alternative units, binary variables for the host (y_{jh}) and the unit selection (z_{ihjd}) are necessary.

Constraint 3 using transformed variables and the big-M formulation for the case of stages with options (stages 2−4) can be expressed as follows

$$v_{jd} \ge \log(S_{ijdh}) + b_i - g_{jd} - M1_{ijdh}(1 - z_{ihjd})$$
$$\forall i, j \in J_h; j \in \text{Alt}; d \in D_j; h \in H_i \qquad (28)$$

where $M1_{ijdh}$ is given by

$$M1_{ijdh} = -v_{jd}^{lo} + \log(S_{ijdh}) + b_i^{up} - g_{jd}^{lo}$$
$$\forall i, j \in J_h; j \in \text{Alt}; d \in D_j; h \in H_i \qquad (29)$$

Superscripts lo and up correspond to lower and upper bounds of the respective variables.

For the case of stages without alternatives, constraint 3 is expressed as

$$v_{jd} \ge \log(S_{ijdh}) + b_i - g_{jd} - M2_{ijdh}(1 - y_{ih})$$
$$\forall i, j \in J_h; j \notin \text{Alt}; d \in D_j; h \in H_i \qquad (30)$$

where $M2_{ijdh}$ is also calculated by means of expression 29. Similar expressions must be posed for stages 10, 12, and 14 corresponding to the chromatographs.

For expression 19 to determine the cycle time, different cases are presented according to the expression for the time, which depends on the type of unit and whether the stage has alternatives. It is convenient to highlight that we could work with a more general expression to

comprise all stages, but such an approach would be less advantageous. First, unnecessary binary variables would be added, as occurred in the previous case with restrictions 28 and 30. Second, this makes it easier to pose many constraints as linear expressions, using more adjusted values for the big-M bound being used.

Stages 1, 5, 7, 8, and 14 do not have alternatives and have constant time. Therefore

$$\text{tl}_i \ge \log(T^0_{ihjd}) - m_{jd} - M3_{ihjd}(1 - y_{ih})$$
$$\forall i, h \in H_i; j \in \{1, 5, 7, 8, 14\}; d \in D_j \qquad (31)$$

with $M3_{ihjd}$ given by

$$M3_{ijdh} = -\text{tl}_i^{lo} + \log(t^0_{ihjd}) - m_{jd}^{lo}$$
$$\forall i, h \in H_i; j \in \{1, 5, 7, 8, 14\}; d \in D_j \qquad (32)$$

For stages 6, 9, 11, 13, and 15, even though time is not constant, the following linear expression holds

$$\text{tl}_i \ge \log(T^1_{ihjd}) + b_i - r_{jd} - g_{jd} - m_{jd} - M4_{ihjd}(1 - y_{ih})$$
$$\forall i, h \in H_i; j \in \{6, 9, 11, 13, 15\}; d \in D_j \qquad (33)$$

where r_{jd} is obtained by applying the same transformation used in eq 8 for V_{jd}, but for the variable R_{jd}. The value of $M4_{ihjd}$ is given by

$$M4_{ihjd} = -\text{tl}_i^{lo} + \log(T^1_{ihjd}) + b_i^{up} - r_{jd}^{lo} - g_{jd}^{lo} - m_{jd}^{lo}$$
$$\forall i, h \in H_i; j \in \{6, 9, 11, 13, 15\}; d \in D_j \qquad (34)$$

Stages 12 and 14 do not have alternatives, but they present a nonlinear expression for time. The following equation is used

$$\exp(\text{tl}_i + m_{jd}) \ge T^0_{ihjd} + T^1_{ihjd} \exp(b_i - g_{jd} - r_{jd}) - M5_{ihjd}(1 - y_{ih})$$
$$\forall i, h \in H_i; j \in \{12, 14\}; d \in D_j \qquad (35)$$

The value of $M5_{ihjd}$ is given by

$$M5_{ihjd} = T^0_{ihjd} \exp(-\text{tl}_i^{lo} - m_{jd}^{lo}) + T^1_{ihjd} \exp(b_i^{up} - g_{jd}^{lo} - r_{jd}^{lo} - m_{jd}^{lo} - \text{tl}_i^{lo}) - 1$$
$$\forall i, h \in H_i; j \in \{12, 14\}; d \in D_j \qquad (36)$$

Finally, for stages 2−4, binary variable z_{ihjd} is used to select equipment for each stage. The expression to determine the limit cycle time in this case is

$$\text{tl}_i \ge \log(T^1_{ihjd}) + b_i - r_{jd} - g_{jd} - m_{jd} - M6_{ihjd}(1 - z_{ihjd}) \quad \forall i, h \in H_i; j \in \text{Alt}; d \in D_j \qquad (37)$$

where $M6_{ihjd}$ is given by expression 34.

Constraint 6 using transformed variables is

$$\sum_i Q_i \exp(\text{tl}_i - b_i) \le H \qquad (38)$$

Condition 7 that relates logic variables Y_{ih} and Z_{ihjd} is mathematically expressed by means of the following set of conditions

$$\sum_{\substack{h \\ h \in H_i}} y_{ih} = 1 \qquad \forall i \tag{39}$$

$$\sum_{\substack{d \\ d \in D_j}} z_{ihjd} \leq 1 \qquad \forall i,\, h \in H_i;\, j \in J_h \tag{40}$$

$$1 - y_{ih} + \sum_{\substack{d \\ d \in D_j}} z_{ihjd} \geq 1 \qquad \forall i,\, h \in H_i;\, j \in J_h \tag{41}$$

$$1 - z_{ihjd} + y_{ih} \geq 1 \qquad \forall i,\, h \in h_i;\, j \in J_h;\, d \in D_j \tag{42}$$

Constraint 39 requires the host selection for each product. Expression 40 ensures that, among all available alternatives at a particular stage, at most one option must be chosen for product i. The case in which no option is chosen occurs when, for example, that stage is not used for that host and therefore no equipment must be chosen. Conditions 41 and 42 relate the two sets of variables and were derived from Vecchietti and Grossmann.[14]

The MINLP model obtained by applying the big-M formulation to the originally posed problem with generalized disjunctive programming is to minimize objective function 27 subject to constraints 13−16, 28, 30, 31, 33, 35, 37−42. Bound constraints on the involved variables must be also considered.

Results with the Big-M Formulation. The software DICOPT++ included in the GAMS optimization pack[17] was used to solve the reformulated big-M MINLP problem. The algorithm used by DICOPT++ is the outer approximation/equality relaxation/augmented penalty (OA/ER/AP) method.[18] The problem was solved on a PC with an Intel Celeron 650-MHz processor and required 43 s.

It should be noted that, to improve the resolution performance, some modifications were made to the proposed model because it gave poor performance. The basis of the OA/ER/AP method is to solve an alternate sequence of MILP master problems and NLP subproblems. In the former, a linear approximation of the original model is solved. The nonlinear model is solved by fixing the binary variables to the values obtained in the MILP master problem solution. In the optimal solution of the NLP, a new linear approximation is generated for the next MILP. In this example and for the original model, many MILP solutions correspond to unfeasible points of the NLP problem. The MILP solution proposes a set of hosts for the products, determines the unit selection for those stages that present alternatives, and sets the number of units operating in parallel in-phase and out-of-phase at each stage. Unfeasibility arises from constraint 38 because the time horizon is not sufficient to process the required demands. The resolution performance is greatly improved if that constraint is modified to the form

$$\sum_i Q_i \exp(tl_i - b_i) \leq H + \rho \tag{43}$$

where ρ is a variable corresponding to the time spent

Table 9. Product Results

product	host used	B_i	TL_i
INS	*E. coli*	3.86	5.00
HBV	yeast (intracellular)	3.19	7.72
TPA	*E. coli*	0.24	12.00
SOD	yeast (intracellular)	2.71	15.44

Table 10. Equipment Results

	item size			duplicated units	
stage	first batch	semicontinuous	second batch	in-phase	out-of-phase
1	1.239	−	−	1	5
2B	1.239	0.567	0.200	1	1
3B	0.619	0.213	−	1	1
4B	0.619	0.886	0.383	1	1
5	1.890	−	−	1	2
6	1.890	26.455	−	1	1
7	2.268	−	−	1	3
8	12.485	−	−	1	3
9	4.162	39.683	−	3	1
10	0.571	0.750	1.594	5	1
11	7.969	25.810	−	1	1
12	0.200	0.750	1.594	5	2
13	3.984	25.810	−	2	1
14	0.200	0.643	0.200	3	1
15	0.386	0.771	0.386	1	1

over the available time horizon. The objective function is modified to be

$$\min \text{cost} = \sum_j \sum_{\substack{d \\ d \in D_j}} \alpha_{jd} \exp(m_{jd} + g_{jd} + \beta_{jd} v_{jd}) + \omega \rho \tag{44}$$

with ω being an appropriate weight. By replacing constraint 38 by constraint 43 and the cost function by eq 44, all solutions generated by the MILP master problem correspond to feasible solutions of the NLP. ρ must be zero in the final solution.

This example was solved for a 6000-h time horizon H, giving a minimum of \$ 6,308,314. Table 9 presents results for each product, indicating the chosen host, batch size, and cycle time. Table 10 reports the results for the stages. It also indicates each unit's dimensions and the number of in-phase and out-of-phase duplicated units. Figure 4 shows the final configuration of the plant, where overlapping duplicated units correspond to in-phase units and those that are not overlapping correspond to out-of-phase units.

It should be pointed out that two hosts were selected, which was the minimal necessary quantity because no host could cover the production of all products. Despite requiring more production stages than the others, one of the hosts used was *Escherichia coli*. As regards stages 2-4 for which the selection of different alternatives for their execution was possible, the same alternatives were selected for the three products. This could be expected a priori because, if different products had used different options, the plant cost would have increased.

It is interesting to note that the possibility of duplication, either in-phase or out of-phase, was employed at several stages and even the combination of the two options, as, for example, in stage 12. Out-of-phase duplication was used to reduce the cycle time, whereas in-phase duplication was mainly used to allow the processing of larger batches. For example, at stage 12, in the case of HBV, the host selected was intracellular yeast, and the corresponding operation time was 15.44 h. When two groups of out-of-phase units are used, that
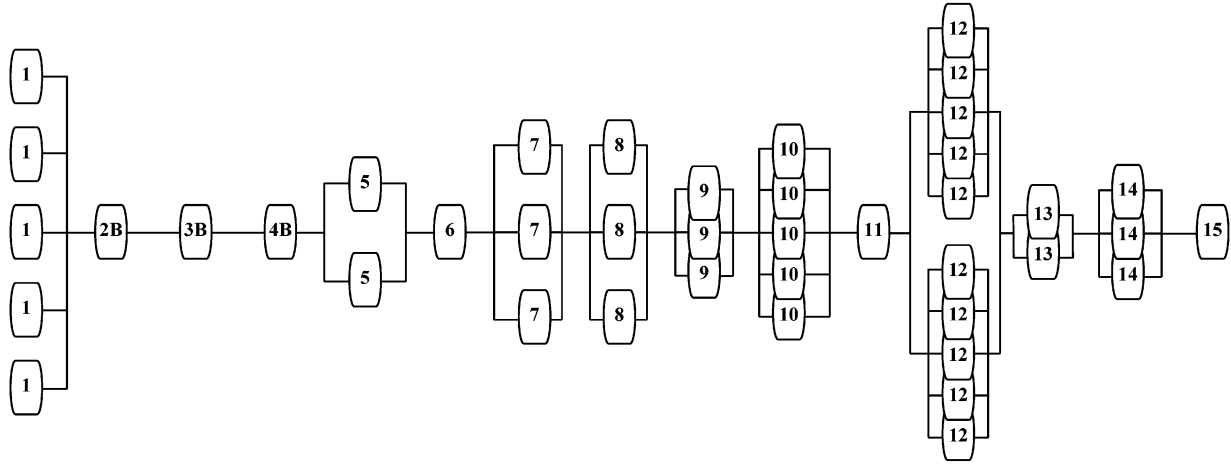
Figure 4. Optimal plant configuration.

time is divided by 2, resulting a stage time of 7.72 h, which coincides with the cycle time obtained for that product. A unit area of 3.75 m² is required considering that the size factor for the chromatographic column included in that stage is 1.1765 and the batch size for the same product is 3.1875 kg. Moreover, because the upper bound for the area of a chromatographic column is 0.75 m², five in-phase duplicated units are required to complete that batch processing.

Convex Hull Formulation

The convex hull relaxation for disjunctive set 20 is expressed by means of the following set of restrictions[19]

$$x - \sum_i v_i = 0 \qquad x, \, v_i \in R^n \qquad (45)$$

$$a_i^{\mathrm{T}} v_i - b_i y_i \leq 0 \qquad i \in D \qquad (46)$$

$$0 \leq v_i \leq v_i^{\mathrm{up}} y_i \qquad i \in D \qquad (47)$$

where eq 22 completes the set. It is important to note that, whereas the big-M relaxation add one constraint to the original formulation, for the convex hull relaxation, the continuous variables x are disaggregated into new variables v_i, and new equations are added. Compared to the big-M relaxation, this can lead to a large number of variables and constraints, especially if there are many disjunctions, which becomes important for problems of large size.

The convex hull relaxation for nonlinear disjunctive set 24 is expressed by the constraint[12]

$$y_i h_i(v_i/y_i) \leq 0 \qquad i \in D \qquad (48)$$

plus constraints 22, 45, and 47. The previous expressions define a convex set in the space of (x, v, y), having v_i^{up} as a valid upper bound for the disaggregated variables. For practical purposes and to avoid division by zero, the variable y_i is replaced by $y_i + \epsilon$, where the scalar ϵ is introduces a small tolerance.

Convex Hull Reformulation Model for the Biotechnological Process

In this section, the convex hull reformulation model is presented. The most important equations and constraints that this reformulation generates are also described.

The objective function is the same as that used in the big-M model, eq 27.

First, we separate the stages into those having alternative units and those with no options. The stages having alternative units are modeled through the following constraints

$$\mathrm{vc}_{jdih} - \mathrm{bd}_{ihjd} + \mathrm{gc}_{jdih} \geq \log(S_{ijdh}) z_{ihjd}$$
$$\forall i, j \in J_h; \, j \in \mathrm{Alt}; \, d \in D_j; \, h \in H_i \quad (49)$$

$$v_{jd} \geq \sum_{h \in H_i} \mathrm{vc}_{jdih} \qquad \forall i, j \in J_h; \, d \in D_j \qquad (50)$$

$$\mathrm{vc}_{jdih} \geq v_{jd}^{\mathrm{lo}} z_{ijdh} \qquad \forall i, j \in J_h; \, j \in \mathrm{Alt}; \, d \in D_j; \, h \in H_i \quad (51)$$

$$\mathrm{vc}_{jdih} \leq v_{jd}^{\mathrm{up}} z_{ihjd} \qquad \forall i, j \in J_h; \, j \in \mathrm{Alt}; \, d \in D_j; \, h \in H_i \quad (52)$$

$$\mathrm{bh}_{ih} = \sum_{d \in D_j} \mathrm{bd}_{ihjd} \qquad \forall i, j \in J_h; \, j \in \mathrm{Alt}; \, h \in H_i \quad (53)$$

$$\mathrm{bd}_{ihjd} \leq b_{ih}^{\mathrm{up}} z_{ijdh} \qquad \forall i, j \in J_h; \, j \in \mathrm{Alt}; \, d \in D_j; \, h \in H_i \quad (54)$$

$$\mathrm{bh}_{ih} \leq \mathrm{bh}_{ih}^{\mathrm{up}} y_{ih} \qquad \forall i, h \in H_i \qquad (55)$$

$$b_i = \sum_{h \in H_i} \mathrm{bh}_{ih} \qquad \forall i \qquad (56)$$

$$\mathrm{gc}_{jdih} \leq g_{jd}^{\mathrm{up}} z_{ihjd} \qquad \forall i, j \in J_h; \, j \in \mathrm{Alt}; \, d \in D_j; \, h \in H_i \quad (57)$$

$$g_{jd} \geq \sum_{h \in H_i} \mathrm{gc}_{jdih} \qquad \forall i, j \in J_h; \, d \in D_j \qquad (58)$$

where vc_{jdih}, gc_{jdih}, and bc_{ihjd} correspond to the batch unit volume, the number of duplicated units operating in-phase, and the batch size, respectively, for stage j, product i, host h, and unit option d. In the case of the batch size, these dimensions must be related to those obtained for the other stages without options for the same product and host, i.e., bh_{ih} (constraint 53). Finally, considering the different hosts available for product i, we can determine the batch size for this produbt, b_i (constraint 56). The decision is made by selecting the host for product i (constraint 55). For the case of variable gc_{jdih} (number of units in operating parallel), only the upper bound is considered because the lower bound assumes the value of 1 for the original variable and 0 for the transformed variable.

Constraint 50 is different from constraint 45: we have an inequality because the same unit is used for all of the products produced by the plant. Therefore, the equality holds for the limiting product that determines the maximum processing capacity for that stage. The same reasoning can be derived for the case of the number of units operating in parallel in-phase, constraint 58.

For those stages without unit options, constraints similar to 49 are written using the binary variable y_{ih}. To simplify the presentation, we use the same variable names as used previously, but it must be pointed out that the subscript d has only one possible value for this case.

$$\mathrm{vc}_{jdih} - \mathrm{bh}_{ih} + \mathrm{gc}_{jdih} \geq \log(S_{ijdh})y_{ih}$$
$$\forall i, j \in J_h; j \notin \mathrm{Alt}; d \in D_j; h \in H_i \quad (59)$$

$$\mathrm{vc}_{jdih} \geq v_{jd}^{\mathrm{lo}}y_{ih} \quad \forall i, j \in J_h; j \notin \mathrm{Alt}; d \in D_j; h \in H_i \quad (60)$$

$$\mathrm{vc}_{jdih} \leq v_{jd}^{\mathrm{up}}y_{ih} \quad \forall i, j \in J_h; j \notin \mathrm{Alt}; d \in D_j; h \in H_i \quad (61)$$

$$\mathrm{gc}_{jdih} \leq g_{jd}^{\mathrm{up}}y_{ih} \quad \forall i, j \in J_h; j \notin \mathrm{Alt}; d \in D_j; h \in H_i \quad (62)$$

Equations 50 and 58 apply to all stages.

We have different expressions when considering the limiting cycle time constraints. The time expression is linear for stages 1, 5, 7, 8, and 14 for which no alternative units exist. This is the case also for stages 10 and 12, but the limiting cycle time expression is nonlinear and the convex hull for the nonlinear case must be used for this case. Finally, stages 2−4 present alternative units for their operation. For these stages, the z_{ihjd} variables must be used instead of y_{ih}. The set of constraints that can be defined for the limiting cycle time is

$$\mathrm{tlh}_{ih} + \mathrm{mc}_{jdih} \geq \log(T_{ihjd}^0)y_{ih}$$
$$\forall i, h \in H_i; j \in \{1, 5, 7, 8, 14\}; d \in D_j \quad (63)$$

$$\mathrm{tlh}_{ih} - \mathrm{bh}_{ih} + \mathrm{rc}_{jdih} + \mathrm{gc}_{jdih} + \mathrm{mc}_{jdih} \geq \log(T_{ihjd}^1)y_{ih}$$
$$\forall i, h \in H_i; j \in \{6, 9, 11, 13, 15\}; d \in D_j \quad (64)$$

$$(\lambda_{ih})\left[T_{ihjd}^0 \exp\left(-\frac{\mathrm{tlh}_{ih}}{\lambda_{ih} + \epsilon} - \frac{\mathrm{mc}_{jdih}}{\lambda_{ih} + \epsilon} \right) + T_{ihjd}^1 \right.$$
$$\exp\left(\frac{\mathrm{bh}_{ih}}{\lambda_{ih} + \epsilon} - \frac{\mathrm{gc}_{jdih}}{\lambda_{ih} + \epsilon} - \frac{\mathrm{rc}_{jdih}}{\lambda_{ih} + \epsilon} - \frac{\mathrm{tlh}_{ih}}{\lambda_{ih} + \epsilon} - \frac{\mathrm{mc}_{jdih}}{\lambda_{ih} + \epsilon} \right) -$$
$$\left. 1 \right] \leq 0 \quad \forall i, h \in H_i; j \in \{10, 12\}; d \in D_j \quad (65)$$

$$y_{ih} = \lambda_{ih} \quad \forall i, h \in H_i \quad (66)$$

$$\mathrm{tld}_{ihjd} - \mathrm{bd}_{ihjd} + \mathrm{rc}_{jdih} + \mathrm{gc}_{jdih} + \mathrm{mc}_{jdih} \geq$$
$$\log(T_{ihjd}^1)z_{ihjd} \quad \forall i, h \in H_i; j \in Alt; d \in D_j \quad (67)$$

$$\mathrm{tlh}_{ih} \leq \mathrm{tl}_i^{\mathrm{up}}y_{ih} \quad \forall i, h \in H_i \quad (68)$$

$$\mathrm{tld}_{ihjd} \leq \mathrm{tl}_i^{\mathrm{up}}z_{ihjd} \quad \forall i, j \in J_h; j \in \mathrm{Alt}; d \in D_j; h \in H_i \quad (69)$$

$$\mathrm{tlh}_{ih} \geq \sum_{d \in D_j} \mathrm{tld}_{ihjd} \quad \forall i, j \in J_h; j \in \mathrm{Alt}; h \in H_i \quad (70)$$

$$\mathrm{tl}_i = \sum_{h \in H_i} \mathrm{tlh}_{ih} \quad \forall i \quad (71)$$

$$\mathrm{mc}_{jdih} \leq m_{jd}^{\mathrm{up}}z_{ihjd} \quad \forall i, j \in J_h; j \in \mathrm{Alt}; d \in D_j; h \in H_i \quad (72)$$

$$\mathrm{mc}_{jdih} \leq m_{jd}^{\mathrm{up}}y_{ih} \quad \forall i, j \in J_h; j \notin \mathrm{Alt}; d \in D_j; h \in H_i \quad (73)$$

$$m_{jd} \geq \sum_{h \in H_i} \mathrm{mc}_{jdih} \quad \forall i, j \in J_h; d \in D_j \quad (74)$$

$$r_{jd} \geq \sum_{h \in H_i} \mathrm{rc}_{jdih} \quad \forall i, j \in J_h; d \in D_j; j \in \mathrm{Sem} \quad (75)$$

$$\mathrm{rc}_{jdih} \geq r_{jd}^{\mathrm{lo}}z_{ihjd} \quad \forall i, j \in J_h; j \in \mathrm{Alt}; d \in D_j; h \in H_i \quad (76)$$

$$\mathrm{rc}_{jdih} \leq r_{jd}^{\mathrm{up}}z_{ihjd} \quad \forall i, j \in J_h; j \in \mathrm{Alt}; d \in D_j; h \in H_i \quad (77)$$

$$\mathrm{rc}_{jdih} \geq r_{jd}^{\mathrm{lo}}y_{ih}$$
$$\forall i, j \in J_h; j \notin \mathrm{Alt}; j \in \mathrm{Sem}; d \in D_j; h \in H_i \quad (78)$$

$$\mathrm{rc}_{jdih} \leq r_{jd}^{\mathrm{up}}y_{ih}$$
$$\forall i, j \in J_h; j \notin \mathrm{Alt}; j \in \mathrm{Sem}; d \in D_j; h \in H_i \quad (79)$$

where Sem is the set of stages that includes semicontinuous units.

For the area size of the semicontinuous stages 10, 12, and 14, chromatographic columns, the following constraint must be satisfied

$$\mathrm{rc}_{jdih} - \mathrm{bh}_{ih} + \mathrm{gc}_{jdih} \geq \log(\mathrm{SR}_{ijdh})y_{ih}$$
$$\forall i, j \in J_h; j \in \{10, 12, 14\}; d \in D_j; h \in H_i \quad (80)$$

where the previous constraints 75, 78, and 79 must also held.

The convex hull reformulation of the biological synthesis problem consists of objective function 27 subject to constraints 49−80, plus constraint 38 about the horizon time, constraints 39−42 involving relationships between binary variables, and constraints 13−16 determining the number of units operating in parallel.

Results with the Convex Hull Formulation. The methodology used to solve the problem was the same as that employed with the big-M reformulation. It must be pointed out that constraint 65 was solved using $\epsilon = 10^{-11}$. Larger values of ϵ did not allow problem convergence or resulted in poor performance in reaching the solution. The optimal value for the objective function is the same as in the previous reformulation. Tables 9 and 10 and Figure 4 show the solution obtained.

Comparing the Reformulations. Table 11 compares the two approaches. The big-M reformulation requires, as was pointed out, a lower number of variables and constraints. However, the solution of the relaxed MINLP (initial solution) is worse than that obtained with the convex hull reformulated problem. The solution time is lower for the convex hull case despite the larger numbers of equations and variables. The explanation for this situation is that the convex hull formulation requires a lower number of iterations to reach the solution, which can be related to the starting

Table 11. Comparison of the Results from the Two Approaches

	big-M	convex hull
optimal solution ($)	6,308,314	6,308,314
resolution time (s)	51,58	29.71
iterations	5	2
solution of relaxed problem	520,801	5,112,746
model equations	507	1705
model variables	344	945
model discrete variables	229	229

point (the relaxed solution), which is closer to the optimal solution of the problem.

Conclusions

A model for the synthesis of a biotechnological process is presented. It is important to analyze the conclusions of this work from different points of view. On one hand, the hierarchical characteristics of the discrete decisions of the model formulated must be considered. First, the host for the elaboration of each product must be selected. In a second level of decision, the equipment to be used to perform the task at each batch stage of the process must be determined. Finally, the number of units to be operated in parallel in-phase or out-of-phase at each stage must be calculated. The disjunctive formulation of this problem allows for an easy and compact representation and visualization of the discrete choices posed.

The next step is the reformulation of the disjunctive problem. The first step was to transform the embedded disjunction defined for the hierarchical discrete decision into the form of a generalized disjunctive problem (GDP). The approach of Vecchietti and Grossmann[14] was used to make this mapping. Once the problem was in the form of a GDP problem, we could reformulate it into a MINLP problem by means of the convex hull or big-M relaxation. The latter is very easy to generate, whereas the convex hull approach requires extra effort because of the numbers of variables and constraints added to the original problem. The capability of software that can perform this task in an automatic way could increase the utilization of this technique to solve optimization problems.

A model taking advantage of process knowledge was generated for each of the approaches. We used this knowledge for the cycle time constraint. Different expressions were posed depending on whether the constraints could be linearized. Simpler equations were used depending on the case.

Regarding the problem reformulation, although the convex hull model was more difficult to generate because it involved more variables and constraints than the big-M approach and these variables and constraints are more difficult to express, it reaches the solution in less CPU time. Depending on the case, it could be better to spend more time on problem generation but obtain a solution faster.

Acknowledgment

Nomenclature

A = area for semicontinuous unit
Alt = set of stages with equipment options

b_i = transformed variable for B_i
B_i = batch size for product i
bd_{ihjd} = batch size for option d stage j with host h for product i
bh_{ih} = batch size for product i with host h
c_k = coefficient in the expression of m_{jd} and g_{jd} with binary variables
D_j = available options for equipment at stage j
D_{ijdh} = duty factor for semicontinuous unit for option d of stage j for product i with host h
g_{jd} = transformed variable for G_{jd}
G_{jd} = number of duplicated units operating in-phase for option d at stage j
gc_{jdih} = number of duplicated units operating in-phase for option d, stage j, with host h for product i
H = time horizon
H_i = available hosts for product i
J_h = stages included in the process with host h
$M1_{ijdh}$ = big-M constant
$M2_{ijdh}$ = big-M constant
$M3_{ijdh}$ = big-M constant
$M4_{ijdh}$ = big-M constant
$M5_{ijdh}$ = big-M constant
$M6_{ijdh}$ = big-M constant
m_{jd} = transformed variable for M_{jd}
M_{jd} = number of duplicated units operating out-of-phase for option d at stage j
mc_{jdih} = number of duplicated units aout-of-phase for option d, stage j, product i, host h
Q_i = demand for product i
r_{jd} = transformed variable for R_{jd}
R = operating rate for semicontinuous unit
R_{jd} = operating rate or area for semicontinuous unit d at stage j
rc_{jdih} = operation rate for semicontinuous unit d at stage j for product i and host h
S_{ijdh} = size factor for product i at stage j with host h and option d
Sem = set of stages with semicontinuous units
SR_{ijdh} = size factor for semicontinuous units at stage j, option d, for product i and host h
T^0_{ijdh} = constant in the expression for the operating time
T^1_{ijdh} = constant in the expression for the operating time
tl_i = transformed variable for TL_i
TL_i = cycle time for product i
tlh_{ih} = cycle time for product i with host h
tld_{ihjd} = cycle time for product i with host h, option d at stage j
v_{jd} = transformed variable for V_{jd}
V = unit size of batch stage
V_{jd} = unit size for stage j, option d
vc_{jdih} = unit size for stage j, option d, with product i, host h
y_{ih} = binary variable that is 1 if host h is used for product i and 0 otherwise
Y_{ih} = Boolean variable that is true if host h is used for product i and false otherwise
yg_{jdk} = binary variable used to represent g_{jd}
ym_{jdk} = binary variable used to represent m_{jd}
z_{ihjd} = binary variable that is 1 if option d is used in stage j for product i and host h and 0 otherwise
Z_{ihjd} = Boolean variable that is true if option d is used in stage j for product i and host h and false otherwise

Subscripts

d = unit option
h = host option
i = product
j = batch stage
k = option for duplicated units

Superscripts

lo = lower bound
up = upper bound

Greek Letters

α_{jd} = coefficient for the cost of units in stage j with option d

β_{jd} = coefficient for the cost of units in stage j with option d

ϵ = parameter in the expression of nonlinear disjunctions

λ_{ih} = variable in the expression of nonlinear disjunctions

θ_{ijdh} = operating time for semicontinuous unit in stage j with option d for product i and host h

ρ = variable corresponding to the time spent over the available time horizon

ω = coefficient for penalty in objective function

Literature Cited

(1) Alvarez, E.; Lienqueo, M.; Pinto, J. Optimal Synthesis of Multistep Protein Purification Processes. *Lat. Am. Appl. Res.* **2001**, *31*, 373−381.

(2) Steffens, M. A.; Fraga, E. S.; Bogle, I. D. L. Synthesis of Bioprocesses Using Physical Properties Data. *Biotechnol. Bioeng.* **2000**, *68*, 218−230.

(3) Grossmann, I. E.; Sargent, R. W. H. Optimal Design of Multipurpose Chemical Plants. *Ind. Eng. Chem. Process Des. Dev.* **1979**, *18*, 343−348.

(4) Knopf, F.; Okos, M.; Reklaitis, G. Optimal Design of Batch/Semicontinuous Processes. *Ind. Eng. Chem. Process Des. Dev.* **1982**, *21*, 79−86.

(5) Modi, A. K.; Karimi, I. A. Design of Multiproduct Batch Processes with Finite Intermediate Storage. *Comput. Chem. Eng.* **1989**, *13*, 127−139.

(6) Salomone, H. E.; Iribarren, O. A. Posynomial Modeling of Batch Plants. *Comput. Chem. Eng.* **1992**, *16*, 173−184.

(7) Salomone, H. E.; Montagna, J. M.; Iribarren, O. A. Dynamic Simulations in the Design of Batch Processes. *Comput. Chem. Eng.* **1994**, *18*, 191−204.

(8) Ravemark, D. E.; Rippin, D. W. T. Optimal Design of Multiproduct Batch Plant. *Comput. Chem. Eng.* **1998**, *22*, 177−183.

(9) Montagna, J. M.; Vecchietti, A. R.; Iribarren, O. A.; Pinto, J. M.; Asenjo, J. A. Optimal Design of Protein Production Plants with Time and Size Factor Process Models. *Biotechnol. Prog.* **2000**, *16*, 228−237.

(10) Pinto, J. M.; Montagna, J. M.; Vecchietti, A. R.; Iribarren O. A.; Asenjo J. A. Process Performance Models in the Optimization of Multiproduct Protein Production Plants. *Biotechnol. Bioeng.* **2001**, *74*, 451−465.

(11) Asenjo, J.; Montagna, J.; Vecchietti, A.; Iribarren, O.; Pinto, J. Strategies for the simultaneous optimization of the structure and the process variables of a protein production plant. *Comput. Chem. Eng.* **2000**, *24*, 2277−2290.

(12) Lee, S.; Grossmann, I. New algorithms for nonlinear generalized disjunctive programming. *Comput. Chem.Eng.* **2000**, *24*, 2125−2142.

(13) Vecchietti, A.; Lee, S.; Grossmann, I. Modeling of discrete/continuous optimization problems: Characterization and formulation of disjunctions and their relaxations. *Comput. Chem. Eng.* **2003**, *27*, 433−448.

(14) Vecchietti, A. R.; Grossmann, I E. Modeling issues and implementation of language for disjunctive programming. *Comput. Chem. Eng.* **2000**, *24*, 2143−2155.

(15) Montagna, J. M.; Vecchietti, A. R. Retrofit of multiproduct batch plants through generalized disjunctive programming. *Math. Comput. Modell.* **2003**, *38*, 465−479.

(16) Iribarren, O.; Montagna, J.; Vecchietti, A.; Pinto, J.; Andrews, B.; Asenjo, J. Optimal Process Synthesis for the Production of Multiple Recombinant Proteins. *Biotechnol. Prog.*, in press.

(17) Brooke, A.; Kendrick, D.; Meeraus A. *GAMS Release 2.25. User's Guide*; The Scientific Press: San Francisco, 1988.

(18) Viswanathan, J.; Grossmann, I. A Combined Penalty Function and Outer Approximation Method for MINLP Optimization. *Comput. Chem. Eng.* **1990**, *14*, 769−782.

(19) Balas, E. Disjunctive programming. Discrete Optimizations II. In *Annals of Discrete Mathematics*; North-Holland: Amsterdam, 1979, Vol. 5; pp 3−51.