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Strategies for the simultaneous optimization of the structure and the process variables of a protein production plant

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Abstract

Process performance models for a multiproduct batch protein plant are used to exploit alternative strategies in the optimization of both the process variables and the structure of the plant. Simple process performance models are used to describe the unit operations, which renders explicit expressions for the size and time factor model in the design of batch plants. In the proposed approach the process variables are optimized regardless the plant structure constraints, which are left as a posterior decision. This optimization is done in a single product-free intermediate storage (SP-FIS) scenario, unbiased with any plant structure. The approach is compared to the case of recipe values for the process variables and to the best optimal solution for the nonconvex mixed integer nonlinear program (MINLP), which arises when simultaneously optimizing the structure and the process variables. This last optimization model is hard to solve and its global solution remains as an open problem. The proposed approach generates solutions very close to the ones obtained from nonconvex MINLP and is quite superior than simply resorting to recipes. We also study the role of process variables in this approach. It is found that they behave as in continuous processes by trading off cost components, with a smooth dependence on the overall cost. Moreover, for feasible designs that include the size and time constraints that correspond to the plant structure, the process variables accommodate the size and time factors to reduce idle times and equipment under-occupancy.

Keywords: Simultaneous optimization; Structure; Process variables; Protein production plant

1. Introduction

The constant time and size factor model (Biegler, Grossmann & Westerberg, 1997; Ravemark & Rippin, 1998) is the most widespread to design multiproduct batch processes. These models are used to optimize the plant design by proper selection of the batch sizes of each product, the operating times of semi-continuous units and the structure of the plant (number of units in parallel at each stage and provision of intermediate storage).

In an alternative approach, process performance models (Salomone & Iribarren, 1992) are used to describe time and size factors as functions of those process variables selected as optimization variables. These process performance models are obtained from the mass balances and kinetic expressions that describe each unit operation. They are kept as simple as possible, yet retaining the influence of the process variables selected to optimize the plant. Salomone and Iribarren (1992) developed the single product case and later Montagna, Iribarren and Galiano (1994) extended this to multiproduct plants. These contributions had in common that the plant structure was given for the problem of optimizing the process variables.

The same mathematical model for plant design is used in both approaches, with the process performance models as additional constraints in the second case. Therefore, the optimization of process variables de-

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pends on the optimization of the structure. To our knowledge, the simultaneous optimization of both the process variables and the structure has not been approached before in the literature.

Barrera and Evans (1989) proposed a multi-level approach where the plant structure is at an upper level, the sizing of units at an intermediate level and the optimization of process variables at a lower level. The authors restricted their case study to the two lower levels, that presented feasibility problems because the optimization at the level of the process variables violated either size constraints imposed at the intermediate level or production targets imposed at the upper level. The particular batch reactor–batch distillation example studied by Barrera and Evans received much attention in the literature, but in this case structural optimization is quite simple, since it refers to the separation network synthesis or the recycle of intermediate cuts, and not to parallel unit processing or provision of intermediate storage.

Recently, Allgor, Evans and Barton (1999) described the multi-level approach as a sequence of ad hoc iterations between the structural and process variable optimization subproblems. These authors propose screening models based on the bounds of process variables to optimize the structure of the plant, for the particular batch reactor–batch distillation process.

In the present paper, we exploit alternative strategies for the simultaneous optimization of the process variables and the structure of a protein plant. In a simpler approach we propose assigning values for the process variables, which sets the size and time factors that can be used to optimize the batch plant structure with the traditional fixed factor model. Then, we propose to first optimize the process variables disregarding the plant structure. We do this by considering single product-free intermediate storage (SP-FIS) scenarios. In such scenarios, we show that process variables behave as in continuous processes trading off cost components with a smooth dependence of the total cost on the process variables. This is done for each of the process performance variables of a plant that processes four proteins. We analyze these results in the context of previous work, mainly the preliminary process design step devised for continuous processes by Douglas (1988), and the pioneering work by Barrera and Evans (1989), who first addressed the issue of process variables trade off in batch processes.

In the first part of this paper, we briefly describe the process for producing human insulin, vaccine for hepatitis B, chymosin and a cryophilic protease by genetically engineered *Saccharomices cerevisiae*. Then we describe the fixed factor design model that describes this plant, and exemplify how the process performance model was constructed with the fermentor as a typical batch stage and the homogenizer as a typical batch — semi-continuous composite stage.

Following, we present the different approaches for using the process performance models to optimize the plant. Thereafter, we use the process performance models in the SP-FIS scenario to study the role of process variables in the optimization, and analyze the tradeoffs where they are involved. Finally, merits and shortcomings of the approaches are discussed.

2. Process description

Fig. 1 shows the flowsheet of a multiproduct batch plant for the production of human insulin, vaccine for hepatitis B, chymosin and cryophilic protease, produced by genetically engineered *S. cerevisiae*. A more detailed description of the process can be found in Montagna, Vecchietti, Iribarren, Pinto and Asenjo (2000).

Insulin and vaccine are well-established commercial products. The plant shown in Fig. 1 would produce the technical grade products with further purification steps rendering the clinical grade. On the other hand, chymosin and the protease are newer products that could be made in the plant shown in Fig. 1. While there is sufficient information about chymosin, cryophilic protease is still in its development stage and most of the process information has been estimated.

All four proteins are produced as the cells grow in the fermentor. Vaccine and protease are intracellular,

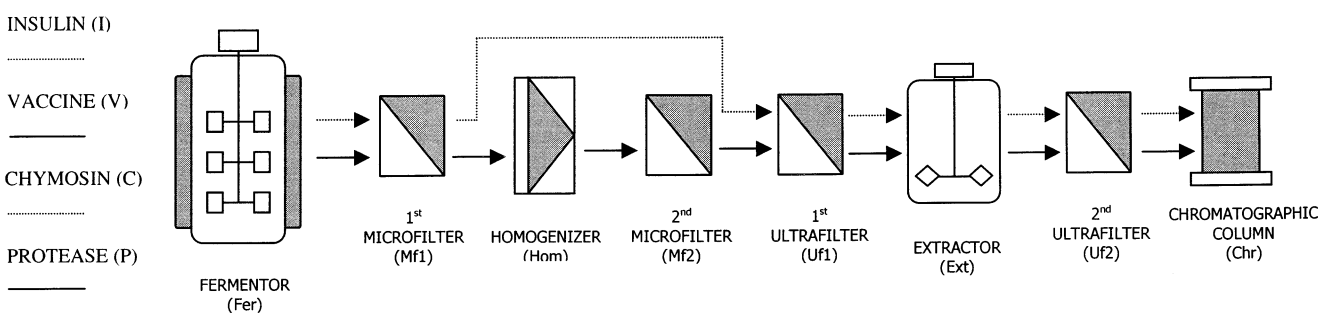

Fig. 1. Flowsheet of the batch plant for the production of proteins.

hence microfilter 1 is used to concentrate the cell suspension, which is afterwards sent to the homogenizer for cell wall disruption and release of the proteins. Microfilter 2 is used to remove the cell debris from the solution of proteins.

The ultrafiltration step prior to the extractor is used for concentrating the solutions in order to minimize the extractor volume. In the liquid–liquid extraction, salt (NaCl) concentration is manipulated to first drive the product to a polyethylene glycol phase (PEG) and back again into an aqueous phosphate solution. In this process, most of the proteins other than the product are removed.

Ultrafiltration is used again for concentrating the solution, and finally the last stage is chromatography where selective binding is used to further separate the product of interest from the remaining proteins.

Insulin and chymosin are extracellular products. These remain in the permeate that crosses the filtration membrane of the first microfilter. In order to reduce the amount of valuable product lost in the retentate, extra water is added to the cell suspension. The filtration operation with make up water is also called diafiltration and dilutes the solution of proteins.

The homogenizer and microfilter for cell debris removal are skipped by the extracellular products, but the ultrafilter is necessary to concentrate the dilute solution prior to extraction. The final steps of extraction, ultrafiltration and chromatography are common to all products.

This example represents a more realistic one than the one in Montagna et al. (1994), who solved a problem with three stages and two products. Larger processes have been solved in the literature resorting to simulation packages as in Mignon and Hernia (1996) for single product plants and fixed plant structures.

3. Fixed factor model for the plant

The general batch process literature (Ravemark, 1995; Biegler et al., 1997; Ravemark & Rippin, 1998) describes batch plants through size and time equations. For batch stages these expressions are as follows:

$$V_j \geq S_{ij} B_i \tag{1}$$

$$T_{ij} = T^0_{ij} + T^1_{ij} B_i \tag{2}$$

In Eq. (1), V_j is the size of each unit at stage j (m^3), B_i is the batch size for product i (kg of product exiting the last stage) and S_{ij} is the size factor of stage j (m^3 required at stage j to produce 1 kg of final product i). In Eq. (2), T_{ij} (h) is the time required at stage j to process a batch of product i and is composed of T^0_{ij} that is a time factor that accounts for fixed time and T^1_{ij}, which accounts for time demands that are proportional to the batch size to be processed. For semi-continuous units the following expression holds:

$$R_j \geq D_{ij} \frac{B_i}{\theta_{ij}} \tag{3}$$

where R_j is the size of the semi-continuous item j, usually a processing rate, as in the case of the homogenizer capacity (m^3/h). In the case of the filtration steps, R_j denotes the filtration area A (m^2). In any case, the sizes are proportional to the batch size B_i (kg) and inversely proportional to the operating time θ_{ij} (h), through a so-called duty factor D_{ij}.

In the case of composite stages with a semi-continuous item that processes the material held in a batch item (as in the case of the homogenizer), we take the model proposed by Salomone, Montagna and Iribarren (1994). The stage is described with Eq. (1) for the batch item size, while the batch processing time T_{ij} includes a fixed downtime T^0_{ij} plus the operating time θ_{ij} of the semi-continuous item, that can be obtained from Eq. (3), which holds as an equality for predicting θ_{ij} once the size of the semi-continuous item R_j has been adopted, as follows:

$$T_{ij} = T^0_{ij} + D_{ij} \frac{B_i}{R_j} \tag{4}$$

Moreover, the following assumptions hold for the optimization model for the design of multiproduct batch plants:

- The plant consists of a sequence of M batch processing stages, which are used to manufacture P different products.
- At each batch stage j there are M_j groups of units in parallel operating out of phase, with each group consisting of N_j units operating in phase.
- Each product i follows the same general processing sequence, admitting only that some stages be skipped. This last case is handled by setting zero values for the size and time factors of the skipped stages. This is an approximation because in the strict sense, this might lead to an overestimation of the schedule (Voudouris & Grossmann, 1996).
- When an intermediate storage tank is not allocated, batches are transferred from one stage to the next without delay, so zero wait policy is considered.
- Intermediate storage tanks of size VT_j may be allocated between batch stages j and $j+1$.
- Production requirements Q_i for each product i in the time horizon H are given.

Some comments about the structure follow. Units are put to work out of phase to overcome time constraints, while operate in phase to overcome size constraints that are given as upper bounds.

The M_j groups of N_j units include the simpler cases of units working out of phase ($N_j = 1$) or in phase ($M_j = 1$). In any case the total number of units at stage j is M_j times N_j with each unit of size V_j.

The structure of the M_jN_j units in parallel in and out of phase is supposed to be the same for all products. Ravemark and Rippin (1998) proposed a more rational approach, which allows a different number of units at each stage as a function of the product. However this approach would require a significant increase in the number of binary variables and therefore was not implemented in the present work.

We also assume that once a storage tank is allocated to position j, it is used by all products in this same location. A more rational approach has been proposed by Vecchietti and Montagna (1998) in which tanks may be used at a different location by each product, but this option also increases significantly the combinatorial aspect of the problem and was not adopted here either.

With the assumptions above, the design problem for the multiproduct batch plant is posed with the objective of minimizing overall capital cost, given by:

$$\text{Min } C = \sum_{j=1}^{M} M_j N_j a_j V_j^{\alpha_j} + \sum_{j=1}^{M} M_j N_j b_j R_j^{\beta_j} + \sum_{j=1}^{M-1} c_j VT_j^{\gamma_j} \tag{5}$$

In Eq. (5) parameters a_j, α_j, b_j, β_j, c_j and γ_j denote appropriate cost coefficients for each item in the plant. The first term on the right hand side corresponds to the batch items, the second to the associate semi-continuous items and the last to the intermediate storage tanks. The summation in the second term holds only for the composite batch stages that contain semi-continuous units (microfilters, homogenizer and ultrafilters).

Batch units must be selected in order to contain the size requirements for all products, which yields:

$$V_j \geq \frac{S_{ij} B_i}{N_j} \qquad \forall i,\ \forall j \tag{6}$$

The operation of the plant is bottlenecked by a cycle time TL_i for each product, which corresponds to the limiting time, i.e. the time between two consecutive batches of this product. Then:

$$TL_i \geq \frac{T_{ij}}{M_j} \qquad \forall i,\ \forall j \tag{7}$$

Over the time horizon H, it is required that the plant processes the given amounts Q_i of each of the P products. Then:

$$\sum_{i=1}^{P} \frac{Q_i TL_i}{B_i} \leq H \tag{8}$$

The allocation of a storage tank decouples the process into two subprocesses upstream and downstream of the tank, so independent batch sizes and limiting cycle times for each subprocess are introduced. Therefore, the (so far) unique B_i is transformed into batch sizes B_{ij} defined for product i at stage j. Moreover, binary variables y_j are introduced, whose value is 1 if an intermediate storage tank is allocated at position j (between stages j and $j+1$) and 0 otherwise.

The size of the intermediate storage tank VT_j is obtained using the following expression from Modi and Karimi (1989):

$$VT_j \geq ST_{ij}(B_{ij} + B_{i,j+1}) - \mathrm{F_{ij}}(1 - \mathrm{y_j})$$
$$\forall i,\ \forall j = 1,\ldots,\ M-1 \tag{9}$$

where F_{ij} is a sufficiently large constant (Big-M constraint), such that the tank volume is relaxed when it is not selected ($y_j = 0$).

Extra constraints are used to model the relationship between the batch size values of consecutive stages (Ravemark, 1995):

$$1 + \left(\frac{1}{\Phi} - 1\right) y_j \leq \frac{B_{ij}}{B_{i,j+1}} \leq 1 + (\Phi - 1)\ y_j$$
$$\forall i,\ \forall j = 1,\ldots,\ M-1 \tag{10}$$

where Φ is an upper bound for the ratio of batch sizes in consecutive stages. In the case that no tank is allocated, constraint (10) enforces consecutive batch sizes to be the same.

In addition, constraints are written to enforce the same productivity for each product at every stage, to avoid accumulation of material in the tanks:

$$\mathrm{Pr}_i = \frac{B_{ij}}{TL_{is}} \qquad j \in s,\ \forall i,\ \forall s \tag{11}$$

In Eq. (11), Pr_i is the production rate of product i and TL_{is} is the limiting cycle time for product i in subprocess s, between two consecutive storage tanks.

Furthermore, there is a set of constraints corresponding to the upper and lower bounds for all variables involved.

Some comments about the implementation and resolution of this fixed factor model follow:

- Eq. (11) replaces TL_i in constraints (7) and (8) in order to simplify the model (Modi & Karimi, 1989).
- The integer variables M_j and N_j are expressed in terms of binary variables, introducing additional integer constraints (Biegler et al., 1997; Ravemark & Rippin, 1998).
- The fixed factor model is a geometric program that can be convexified. Grossmann and Sargent (1979) proved that this model has a unique local optimal solution.
- The resulting MINLP was solved with DICOPT^{++} included in the GAMS optimization modeling software (Brooke, Kendrick & Meeraus, 1992).

4. Process performance models

If the size and time factors in the model presented in the previous section are expressed as constant values, it is necessary to estimate values for every process variable in order to cover the degrees of freedom of the process mass balances, as done for the protein plant in

Montagna et al. (2000). In the approach of the present paper we use as simple as possible process performance models that still retain the influence of the process variables that we a priori expect to have the largest impact on the economics of the process.

Once these variables have been selected, we write the mass balances and kinetic equations that describe each stage by guessing or estimating values for every non-selected process variable, except for the chosen optimization variables. As a result, we obtain analytical expressions for the size and time factors that will be functions of these process variables.

Note that even if the process is new, it usually consists of unit operations that are well known to the designer. At each of them, the extent of separation or of advance of the operation can be described as a function of parameters of both the unit and the material processed, as well as the process variables. The methodology that we are suggesting for selecting suitable unit operations, their interconnections, and a list of dominant design variables (these steps must be performed prior to pose the optimization problem that we address here), is the hierarchical approach described in detail in Douglas (1988).

The process variables that have been selected as optimization variables are as follows: the biomass concentration at the fermentor (X_{fer}) and microfilter 1 (X_{mf1}) for all products, the volumetric ratio of diafiltration water to suspension feed in microfilter 1 (W_{mf1}) for extracellular insulin and chymosin and at microfilter 2 (W_{mf2}) for intracellular vaccine and protease after cell disruption, the number of passes through the homogenizer (N_{p}) for intracellular vaccine and protease, and the volumetric ratio (R) of PEG to phosphate phases in the extractor for all products.

Following is a brief description of the process performance models for the Fermentor as a typical batch stage, and for the homogenizer as a typical composite batch-semi-continuous stage. Most of the information needed to develop them was taken from Asenjo (1990) and Belter, Cussler and Hu (1988). A more detailed description as well as the process performance models of the protein plant can be found in Pinto, Montagna, Vecchietti, Iribarren and Asenjo (2000).

4.1. Fermentor

A kinetic mechanism constrained by a maximum biomass concentration is assumed for cell growth (logistic equation):

$$\frac{\mathrm{d}X_{i,\,\text{fer}}}{\mathrm{d}t} = \phi X_{i\,\text{fer}}\left(1 - \frac{X_{i,\,\text{fer}}}{X_{\max}}\right) \qquad \forall i \tag{12}$$

We estimate the same kinetic constant $\phi = 0.263\ \text{h}^{-1}$ and maximum biomass concentration $X_{\max} = 55\ \text{kg/m}^3$ for all products (Atkinson & Mavituna, 1983; Montagna et al., 2000). The batch size produced in the Fermentor is related to the fermentation broth volume $V_{i,\,\text{fer}}$ through the biomass concentration as follows:

$$B_{i,\,\text{fer}} = V_{i,\,\text{fer}} X_{\text{fi,\,fer}} k_i \qquad \forall i \tag{13}$$

where k_i is a stoichiometric ratio (kg of product i/kg of biomass) whose value is 0.08 for protease, 0.06 for chymosin, 0.02 for insulin, and 0.04 for vaccine (Montagna et al., 2000). Then, it must be taken into account that the batch size at any stage j is related to the batch size exiting the plant through the yields of all stages between this particular stage and last stage of the plant, as follows:

$$B_i = B_{ij} \prod_{k=j+1}^{M} \eta_{ik} \qquad \forall i,\ \forall j \tag{14}$$

In Eq. (14), η_{ik} denotes the yields of product i at stage k (the ratio of batch size that leaves the stage to the batch size that enters the same stage), M is the total number of stages in the plant, and B_{ij} is the batch size of product i that leaves stage j.

Integrating Eq. (12) between an initial biomass concentration 0.05 $X_{\max}$ (inoculum seeded amounts to 5% of the Fermentor capacity) and $X_{i,\,\text{fer}}$ and adding an estimated downtime of 4 h (1 h for discharging, 2 for sterilizing and 1 for charging), gives the time expressions for the Fermentor as in Eq. (15):

$$T_{i,\,\text{fer}}\ (\text{h}) = 4 + 3.8 \ln\left[\frac{0.35 X_{i,\,\text{fer}}}{1 - \dfrac{X_{i,\,\text{fer}}}{55}}\right] \qquad \forall i \tag{15}$$

Eq. (15) is the same for all products. Note that if $X_{i,\,\text{fer}}$ were set to any value, then the expression would result in a constant time factor; note that by comparing the batch time expression (15) to the general Eq. (2) it can be observed that it has a non-zero value for T_{ij}^0 but $T_{ij}^1 = 0$ (there is no time demand proportional to the batch size). This is typical of operations governed by kinetics (bioreactors, cristallizers).

Recalling that the size factor for the Fermentor is the $V_{i,\,\text{fer}}$ of fermentation broth divided by the B_i (kg of product i exiting the plant), we can get the size factor expression for the Fermentor from Eqs. (13) and (14). For example, in the cases of insulin and chymosin, these are:

$$S_{i,\,\text{fer}}\ (\text{m}^3/\text{kg}) = \frac{1.25}{k_i X_{i,\,\text{fer}} \eta_{i,\,\text{mf1}} \eta_{i,\,\text{ext}} \eta_{i,\,\text{chr}}} \qquad i = \{I, C\} \tag{16}$$

where the factor 1.25 accounts for the fact that the fermentation broth occupies 80% of the fermentor vessel, and that the denominator contains the yield values different from one for extracellular products. Considering that the yields of the stages also depend on the process variables, we have that if these were set at some

value, then the size factor would assume constant values.

4.2. Homogenizer

The vaccine and protease batches pass through the homogenizer for cell disruption. The holding vessel capacity corresponds to the final volume in the retentate vessel of microfilter 1. This yields the following size factor expressions:

$$S_{i,\,\mathrm{hom}}\ (\mathrm{m^3/kg}) = \frac{1.25}{k_i X_{i,\,\mathrm{mf1}} \eta_{i,\,\mathrm{hom}} \eta_{i,\,\mathrm{mf2}} \eta_{i,\,\mathrm{ext}} \eta_{i,\,\mathrm{chr}}}$$

$$i = \{P, V\} \tag{17}$$

The denominator of (17) contains the yields other than one, for the intracellular products. The time required to homogenize is proportional to the volume fed to the homogenizer $V_{i,\,\mathrm{hom}}$ ($\mathrm{m^3}$) and inversely proportional to the homogenizer capacity cap ($\mathrm{m^3/h}$) plus a downtime:

$$T_{i,\,\mathrm{hom}} = T^0_{i,\,\mathrm{hom}} = \frac{V_{i,\,\mathrm{hom}}}{\mathrm{Cap}} \qquad i = \{P, V\} \tag{18}$$

The volume fed to the homogenizer is the batch volume times the number of passes through the homogenizer N_p, and estimating a 1.25 h downtime (25 min for each discharging, cleaning and charging) yields the time expressions for the homogenizer:

$$T_{i,\mathrm{hom}}\ (h) = 1.25 + \left[\frac{Np_i}{k_i X_{i,\,\mathrm{mf1}} \eta_{i,\,\mathrm{hom}} \eta_{i,\,\mathrm{mf2}} \eta_{i,\,\mathrm{ext}} \eta_{i,\,\mathrm{chr}}}\right] \frac{B_i}{\mathrm{Cap}}$$

$$i = \{P, V\} \tag{19}$$

Observe that in the numerator inside the brackets, we replaced 1.25 by 1 because we are considering the batch volume without incrementing it due to the 80% vessel occupancy. By comparing Eq. (19) with Eq. (4), it can be seen that the term inside brackets is the duty factor for the homogenizer.

Successive passes through the homogenizer drive the fraction of cells disrupted asymptotically to 1 through a first order law. This is also the fraction of proteins released Fr_i, expressed as in Eq. (20):

$$Fr_i = 1 - \exp(-k_1 Np_i) \qquad i = \{P, V\} \tag{20}$$

where k_1 is a constant that measures how labile is the microorganism and Np_i the number of passes through the homogenizer. The same law can be used to estimate the fraction of released proteins that are denatured Fd_i:

$$Fd_i = 1 - \exp(-k_2 Np_i) \qquad i = \{P, V\} \tag{21}$$

where k_2 measures how labile is the product. k_1 is larger than k_2 because larger particles are more easily disrupted. We estimate these constants to be $k_1 = 1.5$ and $k_2 = 0.03$ (Engler, 1990). While it is correct that k_1 be the same for both protease and vaccine because the element being disrupted is the same yeast, k_2 should be experimentally found for each product. Here we took a single figure for k_2 which is a typical value for proteins. The yield in the homogenizer is the fraction released times the fraction not denatured:

$$\eta_{i,\mathrm{hom}} = Fr_i(1 - Fd_i) \qquad i = \{P, V\} \tag{22}$$

Replacing Eqs. (20) and (21) into Eq. (22) results in the yield for the homogenizer:

$$\eta_{i,\mathrm{hom}} = [1 - \exp(-1.5 Np_i)] \exp(-0.03 Np_i)$$

$$i = \{P, V\} \tag{23}$$

Again, note that by setting a value for the process variables Np_i would provide a constant value for the yield in Eq. (23). Similar expressions are obtained for the size factor, time factor and yield of every other stage of the protein production plant in Pinto et al. (2000).

5. Proposed optimization approaches

The traditional geometric program used for the multiproduct batch plant design only considers fixed values for size and time factors. Now, having process performance models such as the ones described in the previous section, we may address different options in order to include the effect of the process variables in the search for the optimal design.

5.1. The non convex MINLP approach

The more rigorous form to include the process performance models in the mathematical program is to combine the traditional geometric program (where the size and time factors are previously fixed) and the process performance models, that describe each of these factors as functions of the process variables.

As a whole, this is a MINLP, which lacks a definite structure, just because the nonlinear process performance models depend on the particular unit operations involved in the process at hand. The global optimization of this problem, which most likely have multiple local optima, is still an open problem, and it is included as one of the challenges in global optimization, in a recent review by Floudas and Pardalos (1999).

5.2. Hierarchical approaches

Douglas (1985, 1988) presented a hierarchical approach for designing continuous processes, which is based on a sequence of decisions of decreasing level of economic impact and increasing level of detail. Once the methodology reaches to the point of generating alternative process flowsheets, they are evaluated resorting to simplified unit operation models to size and cost the alternatives.

We present and compare two alternative approaches for including the process performance models to obtain improved solutions to the multiproduct batch plant design. In both cases we decompose the problem. First, we assign values to the process variables, i.e. we construct the recipe for the processes. Then, we use this set of process variables and the resulting size and time factors to optimize the structure of the plant with the traditional geometric program.

5.3. First approach: user-provided process variables

We take advantage of the fact that the process performance models permit computing a set of consistent time and size factors. In a very simple strategy, we can guess a set of reasonably good process variables to obtain a consistent set of time and size factors, and then solve the resulting geometric program of the multiproduct plant.

While it is relatively simple to guess reasonable values for the process variables for someone familiar with the unit operations involved in the process, it is not always an easy task to guess a reasonable and consistent set of size and time factors.

5.4. Second approach: optimize the process variables in a constraint–free scenario

The SP-FIS scenario removes all the size and time constraints and so fulfils the objective that the optimization be unbiased with respect to the plant structure, which has been left as a second level decision. The optimal solution of this SP-FIS problem also provides a set of fixed size and time factors to the Geometric MINLP.

To pose the SP-FIS problem, we need to perform an arbitrary, yet as reasonable as possible, partition of the annual operating time among the products that we expect to produce in the same plant and define a production rate Pr_i for each product:

$$\mathrm{Pr}_i\ (kg/h) = \frac{Q_i\ (kg)}{H_i\ (h)} \qquad \forall i \tag{24}$$

where Q_i is the annual target production and H_i the time horizon assigned to each product i. In the case of the protein production plant, the most expensive stage is fermentation, so a reasonable partition of the total horizon time should consider similar Fermentor size requirements through the stoichiometric ratios k_i. As in our case the biomass production step demands the same amount of time regardless the protein being produced, this criteria leads to assigning the following time horizon for each product:

$$H_i = H\frac{Q_i/k_i}{\sum_i Q_i/k_i} \qquad \forall i \tag{25}$$

This maximal occupancy of the more expensive stage used to be the industrial design practice in the past, as reported in Flatz (1980, 1981).

While the single product assumption relaxes the sizing constraints, the free intermediate storage assumption permits to ignore the time constraints so that each stage works with its own cycle time uninterruptedly, thus satisfying the production rate assigned to the product.

Note that the level of storage that is required is not unlimited, but the decoupling level described in Modi and Karimi (1989), which sizes the tanks to simultaneously hold the batches entering and leaving the tank.

5.5. Comparison of approaches

First, following the first approach presented, we estimated a good set of values for the process variables, which is shown in Table 1. The value chosen for X_{fer} corresponds to 90% total conversion in the Fermentor and X_{mf1} is near its upper bound of 250 kg/m^3. Usual amounts of washing water are of the same order of the feed amount, i.e. $W_{\mathrm{mf1(mf2)}} \approx 1$; moreover, we chose a larger figure for the intracellular products because the feed concentration is higher. Usual values for Np are larger than 1 but seldom larger than 5; finally, 1 is a common choice for R in the laboratory.

The process performance models were used to obtain a consistent set of time and size factors, and then the resulting geometric program was solved for two cases: with and without the allocation of intermediate storage tanks and the possibility of parallel units in both cases.

Second, using the SP-FIS approach, the single product problems were solved with the process performance models included as additional constraints and with the time horizons for each product as given by Eq. (25). These unconstrained NLP (but for bounds on the process variables) are easy to solve, and even if there is no guarantee of unique optimal solutions, no evidence was found on the existence of multiple optima. The optimal values obtained for the process variables are shown in Table 2. This set of process variables was used to obtain the time and size factors for the geometric model of the multiproduct plant, through the process performance models. The geometric program was solved for the two cases presented in the first approach.

Table 1
User-provided values for the process variables

Product	X_{fer}	X_{mf1}	W_{mf1}	W_{mf2}	N_{p}	R
Insulin	50.	200.	1.25	–	–	1.0
Vaccine	50.	200.	-	1.50	3.0	1.0
Chymosin	50.	200.	1.25	–	–	1.0
Protease	50.	200.	–	1.50	3.0	1.0

Table 2
Optimal values of the process variables in the SP-FIS scenario

Product	X_{fer}	X_{mf1}	W_{mf1}	W_{mf2}	N_p	R
Insulin	48.21	250.	0.26	–	–	0.617
Vaccine	46.02	250.	–	1.197	2.566	0.596
Chymosin	48.15	250.	0.25	–	–	0.604
Protease	45.81	250.	–	1.159	2.561	0.608

Finally, the complete non-convex MINLP model was also solved. This problem is quite hard to solve and the solutions presented were obtained after running from several initial points and are not guaranteed to be global optima. The set of optimal values for the process variables is presented in Table 3.

The values of the objective function at the optimal solutions and typical execution times in a PC with Pentium 200 are shown in Table 4, for the three approaches, with and without storage tanks.

Comparing guessed values for the process variables in Table 1 with the optimal values from Tables 2 and 3, we notice that the former were in general near the optimal, with the exception of the amount of washing water at microfilter 1 (W_{mf1}). Despite that, in Table 4 the cost of the alternatives designed with the factors that correspond to the set of optimal variables of the SP-FIS problem is approximately 10% lower than the results of the first approach. Even more importantly, these are very close to the optimal cost of the non-convex MINLP.

In the case of W_{mf1}, the discrepancy between guessed and optimal values was larger than for the other variables. At the optimal solution, X_{mf1} was larger than the guessed value, and at its upper bound, so that the volume of retentate at the end of the filtration step was smaller than expected. So, at the diafiltration stage the washing water added was more effective in recovering the valuable product and so the optimal value was smaller than expected. In any event, this kind of differences between guessed and optimal values were considered rather satisfactory. On the other hand, the differences in other variables were surprisingly small.

In the case of the biomass concentration at microfilter 1 shown in Table 2, the optimal value lies on its upper bound, which lead us to remove it from the list of variables in the MINLP. This was done even if there is no guarantee that it would remain at the same value in the MINLP optimal solution. The usual rule for the membrane concentration steps is to dewater up to an upper bound dictated by physical limitations in the case of a suspension of cells or by protein precipitation in the ultrafilters. We have only proposed one of these final concentrations as an optimization variable (in microfilter 2 and both ultrafilters the models implemented set the final concentrations to these bounds). This was done to illustrate that, if process variables that are not involved in a tradeoff are selected as optimization variables, the optimization step will automatically place them at a bound.

Comparing Table 2 of optimal values of the unconstrained problem with Table 3 of optimal values for

Table 3
Optimal values of the process variables with the non-convex MINLP

Model	Product	X_{fer}	W_{mf1}	W_{mf2}	N_p	R
Without tanks	Insulin	46.54	0.35	–	–	0.636
	Vaccine	38.52	–	1.81	2.36	0.474
	Chymosin	38.96	0.10	–	–	0.634
	Protease	31.26	–	1.75	2.39	0.635
With tanks	Insulin	49.35	0.21	–	–	0.636
	Vaccine	45.54	–	1.31	2.23	0.582
	Chymosin	49.12	0.20	–	–	0.634
	Protease	45.54	–	1.31	2.23	0.582

Table 4
Comparison of optimal solutions

Approach	Storage policy			
	Without storage tanks		With storage tanks	
	Optimal cost ($)	CPU time (s)	Optimal cost ($)	CPU time (s)
User provided-geometric MINLP	1 770 418	12	920 790	17
SP-FIS — geometric MINLP	1 595 305	25	803 329	30
Non-convex MINLP	1 505 326	78	800 138	221

solutions constrained to their respective structures, it should be noticed that the process variables moved away from the unconstrained optimum. The structure with tanks, which is the most cost effective, demanded smaller deviations from the values at the unconstrained optimum. Clearly, the model that allows both units in parallel and storage tanks was the most cost effective. The optimal structure is shown in Fig. 2. It has just one unit per stage and four tanks located after the fermentor, microfilter 2, ultrafilter 1 and ultrafilter 2; no duplication was implemented although this was allowed. The same optimal structure was obtained with all three approaches. When only parallel units are allowed, the optimal structure of the non-convex MINLP model generates a design with five fermentors working out of phase, and two chromatographic columns in phase. The fixed factor models obtained a similar structure with five fermentors out of phase, but three chromatographic columns in phase.

Comparison of the optimal costs shown in Table 4 shows that the optimization of the structure has a much higher impact on the cost than the optimization of the process variables. Optimization of the process variables reduced the cost by 10% when moving from guessed values to the optimal SP-FIS for both structures. Further improvement was obtained when solving the non convex MINLP; 5% for the case without tanks but only 0.5% when tanks are allowed, both with respect to SP-FIS. On the other hand, optimization of the structure, moving from parallel units without storage to the structure with storage and no duplication, reduced the cost of the plant by 50% in the three cases.

In Table 4, in the case of user-provided values for the process variables, the times reported correspond to solving the geometric MINLP. The SP-FIS geometric MINLP approach doubled the execution time, since the optimization of the four SP-FIS problems demanded about 3 s each. The largest Geometric MINLP solved had 285 constraints, which include 90 process performance constraints, and 297 variables, from which 87 were binary. The times reported for the non-convex MINLP are typical figures for just one optimization. Several optimizations were done starting from different initial points in each case.

6. The role of the process variables

In this section we analyze the economic impact of the process variables of the protein production plant, in the SP-FIS scenario. We took the cryophilic protease as an example because, being intracellular, it goes through all the processing stages. First, we optimized the process variables. Then, we plotted the cost items versus each variable, with the remaining variables at their optimal values.

6.1. Biomass concentration in the fermentor X_{fer} (Fig. 3)

Biomass concentration increases monotonically with time, at a decreasing pace as it asymptotically approaches a maximum. On the other hand, production of biomass in the Fermentor reaches a maximum rate at an intermediate value of 45.1 kg/m^3, in agreement with the minimum cost for the fermentor. However, the cost of the downstream process decreases monotonically with the increase in concentration. Consequently, the downstream shifts the overall optimum to a slightly larger concentration value of 45.8 kg/m^3.

6.2. Biomass concentration at microfilter 1 X_{mf1} (Fig. 4)

Higher values of biomass concentration require larger volumes of liquid to be permeated through the membrane. At a constant permeation rate, this requires more area and thus, an increased filter cost. On the other hand, both the homogenizer and microfilter 2 sizes are inversely proportional to this concentration, so their costs decrease monotonically. The optimal biomass concentration is at its upper bound of 250 kg/m^3.

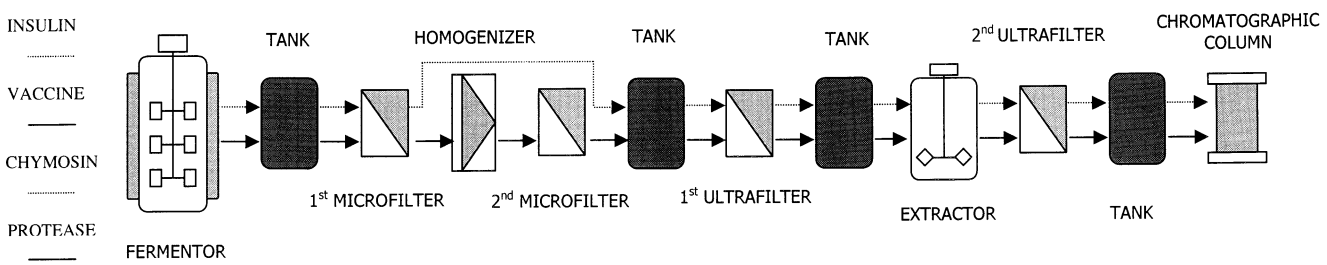

Fig. 2. Optimal plant protein structure with duplication of units and intermediate storage tanks.

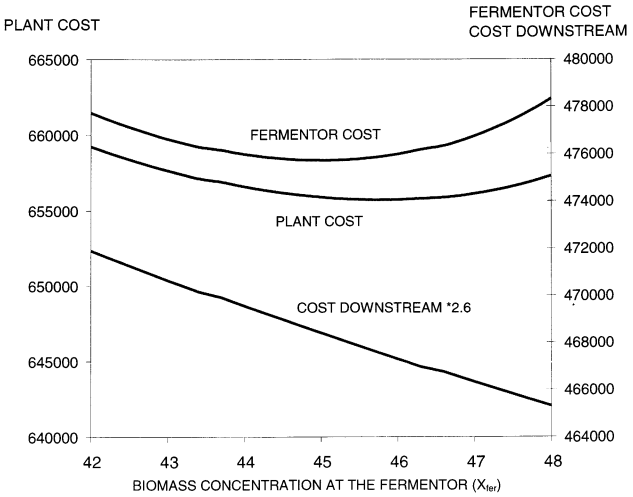

Fig. 3. Tradeoff in the selection of biomass concentration at the fermentor (X_{fer}).

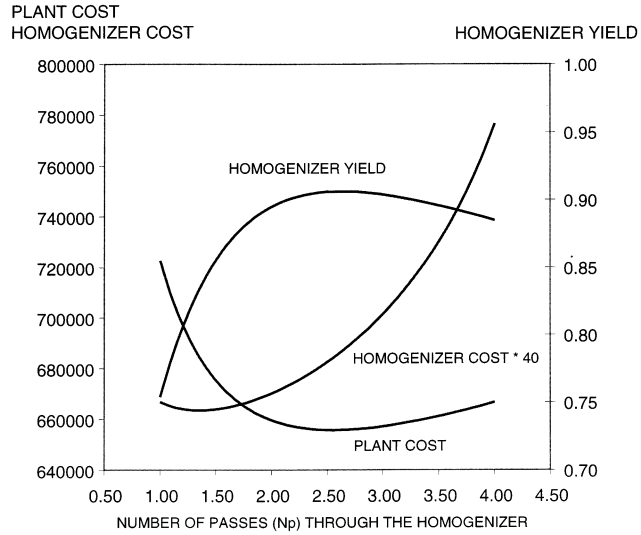

Fig. 5. Tradeoff in the selection of a number of passes (N_p) through the homogenizer.

6.3. Number of passes through the homogenizer Np (Fig. 5)

A larger number of passes through the homogenizer increases the number of cells disrupted (protein released) but also increases the amount of released protein that is being denatured. As a result, there is a maximum yield of product (released but not denatured, with respect to the total amount inside the cells before processing) at $Np = 2.65$ passes.

The size of the homogenizer is proportional to Np and inversely proportional to the yield and has a minimum value at $Np = 1.35$. However, the yield affects the whole plant (specially increasing the size required from the units upstream of the homogenizer). The optimal value for the plant is $Np = 2.55$, which is very close to the maximum yield.

6.4. Ratio of washing water at microfilter 2 W_{mf2} (Fig. 6)

At microfilter 2, the protein already released is recovered by diafiltration with distilled water. An increase in the amount of water increases the size of both microfilter 2 and of ultrafilter 1, whose purpose is to re-concentrate the diluted protein solution.

So the costs of microfilter 2 and ultrafilter 1 increase monotonically (and so does the yield of product in microfilter 2) with W_{mf2}. The increase in yield decreases the size required from the upstream units: fermentor,

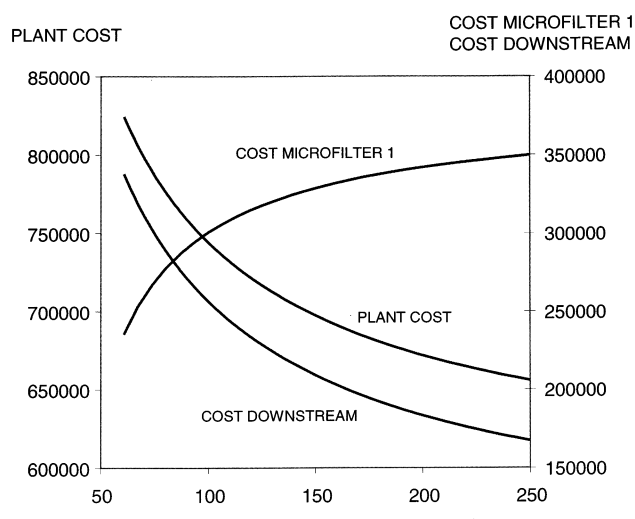

Fig. 4. Tradeoff in the selection of biomass concentration (X_{mf1}) at microfilter 1 (X_{mf1}).

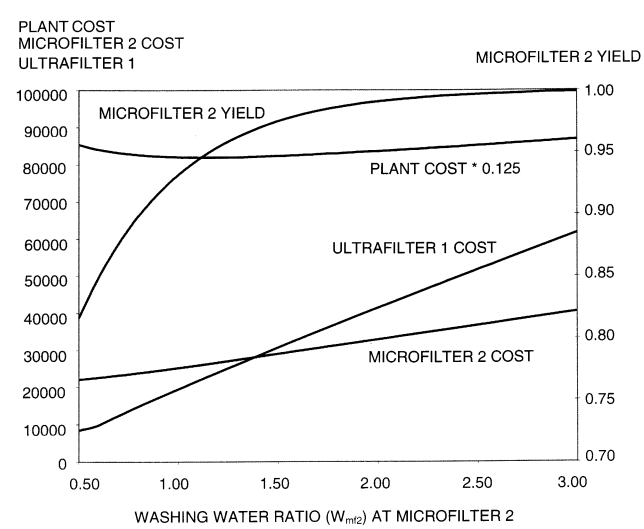

Fig. 6. Tradeoff in the selection of washing water ratio (W_{mf2}) at microfilter 2.

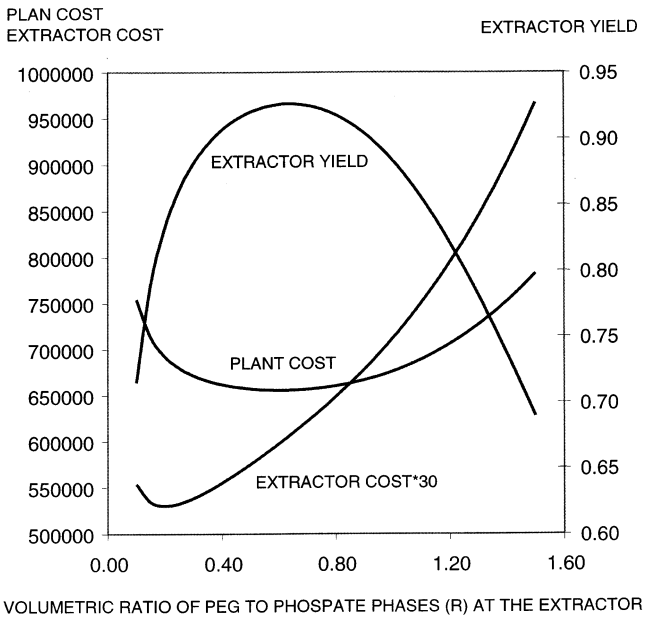

Fig. 7. Tradeoff in the selection of the volumetric ration of PEG to phosphate phases (R) at the extractor.

microfilter 1 and homogenizer. As a result, we have an overall optimum for the plant at a ratio of washing water to feed at $W_{mf2} = 1.15$, which is an intermediate value.

6.5. Volumetric ratio of PEG to phosphate phases R (Fig. 7)

Augmenting the ratio R causes an increase in the yield of the first extraction from the phosphate into the PEG phase, but decreases the yield of the back extraction into the new salt-free Phosphate phase. This occurs because of the smaller amount of the new phase, and because of a poorer dilution of the NaCl that remains in the PEG, which jeopardizes the partition constant for this back extraction. As a result, the overall extraction yield has a maximum at $R = 0.63$.

The cost of the extractor grows linearly with R (R denotes the volume of PEG phase to be added, per volume of the batch entering this stage) and is inversely proportional to the extraction yield. Consequently, the cost of the extractor shows a minimum at a phase ratio of $R = 0.2$. However the extraction yield also affects all the sizes of the upstream stages, so the overall process optimum is at $R = 0.61$ (close to the maximum yield).

6.6. Analysis of the tradeoffs that occur when setting the process variables

Barrera and Evans (1989) published a pioneering work addressing the role of process variables in batch plants. These authors named tradeoffs of the first type those that occur within a single stage, of the second type those that occur between or among stages, and of the third type those that are a combination of the first two types. Their analysis of the tradeoffs presented in batch plants fully applies in our case and it appears to be quite general.

The biomass concentration in microfilter 1 and the washing water ratio in microfilter 2 are involved in tradeoffs of the second type (an increase in these variables increases the costs of these units, but decreases the cost of the units down or up stream). The biomass concentration in the fermentor, the number of passes through the homogenizer and the ratio of PEG to phosphate phases in the extractor, are involved in tradeoffs of the third type. There is a particular value for these variables that produces a minimum cost of the respective stages, but they also affect the cost of other units up or down stream.

More recently, papers dealing with the optimization of process variables in the design of multiproduct batch plants, such as that of Bhatia and Biegler (1996), pose the present problem as a system of algebraic and differential equations. They found that optimizing the individual stages sequentially renders poor results as compared with simultaneous optimization. In the context of the tradeoff analysis, sequential optimization would only succeed in the case that all the tradeoffs were of the first type. Incidentally, no tradeoffs of the first type were found in the Protein Production Plant.

The shapes of the overall cost functions of Figs. 3–7 show an interesting point regarding the role of process variables in the optimization. When the variables produce a minimum cost for the overall process at a value within their allowed range, the shape of these overall cost functions is rather flat around the optima. Thus, the process variables can be moved (which in turn affects the size and time factors) with no major penalty on the overall cost.

An important fraction of the cost of a multiproduct batch plant is due to the idle times and volumetric under-utilization of the process units. This is illustrated in Tables 5 and 6 that compare the idle times of the designs obtained with the User-Provided process variables and with the non-convex MINLP. While the optimization of the process variables reduces the idle times in both cases, in the plant with storage tanks these are smaller as in this case the structure is optimal.

Even if the summation of the unit idle times is a rather arbitrary performance index, it gives an idea of this effect. In Table 5, this index is of 48 h for user provided process variables and is reduced to 32 h when optimizing the variables. In Table 6, with storage tanks, the optimization reduces the overall idle time from 7 to 6 h.

It is also interesting to note that in every case the idle time of the fermentor is zero, thus endorsing the assumption that the more expensive stage is fully utilized. We used this assumption to distribute the horizon time among the products.

7. Conclusions

Process performance models recently developed for a multiproduct batch protein plant have been used to explore alternative optimization strategies and to study the role of process variables in the simultaneous optimization of both the process variables and the structure of the plant. To our knowledge this simultaneous optimization has not been approached before.

The main merit of the optimization approach is its modular structure. The process performance models are additional constraints to the traditional geometric program, which remains unchanged. Setting up models with higher level of detail is highly facilitated; for example one might start implementing a fixed factor model and next incorporate process performance models for selected key-stages.

While it is not trivial to estimate a set of reasonable constant time and size factors, it is easier to guess good values for the process variables. In this sense, the process performance models are able to predict a consistent set of size and time factors as a function of process variables.

A better set of time and size factors was obtained by optimizing the process variables in a single product-free intermediate storage scenario. Furthermore, the plant structures obtained with the fixed factors that correspond to this set were close to the ones obtained with the complete model.

The role of process variables in the optimization was also studied. We find that in the unconstrained SP-FIS scenario they behave as in continuous processes, trading off cost components with a smooth dependence of the total cost on the process variables. Moreover, for feasible designs that include the size and time constraints that correspond to the plant structure, the process variables shift to accommodate the size and time factors to reduce idle times and under-occupancy of equipment.

The complete MINLP that includes the proposed performance models is non-convex and difficult to solve. The optimal solutions obtained are local optima, and future work is needed to address this issue.

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Table 5
Stage idle times (h) without storage tanks

Approach	Product	Fer	Mf1	Hom	Mf2	Uf1	Ext	Uf2	Chr
User Provided Variables	Insulin	0.	0.	–	–	0.01	3.00	2.16	4.37
	Vaccine	0.	2.40	0.	0.	3.26	3.00	0.	4.32
	Chymosin	0.	0.66	–	–	0.	3.00	3.00	4.33
	Protease	0.	2.95	0.13	0.12	3.28	3.00	0.85	4.29
Non-convex MINLP	Insulin	0.	0.	–	–	0.	2.54	2.01	3.92
	Vaccine	0.	0.56	0.	0.03	2.12	1.89	0.	3.24
	Chymosin	0.	0.49	–	–	0.	1.92	2.42	3.28
	Protease	0.	0.81	0.	0.	1.82	1.46	0.74	2.80

Table 6
Stage idle times (h) with storage tanks

Approach	Product	Fer	Mf1	Hom	Mf2	Uf1	Ext	Uf2	Chr
User Provided Variables	Insulin	0.	0.	–	–	0.	0.	0.72	0.93
	Vaccine	0.	1.73	0.	0.	0.	0.	0.	0.27
	Chymosin	0.	0.	–	–	0.	0.	1.00	0.06
	Protease	0.	2.07	0.	0.	0.	0.	0.23	0.
Non-convex MINLP	Insulin	0.	0.	–	–	0.	0.	0.77	0.92
	Vaccine	0.	0.51	0.	0.	0.57	0.	0.	0.25
	Chymosin	0.	0.51	–	–	0.	0.	1.05	0.02
	Protease	0.	1.15	0.	0.	0.	0.	0.26	0.

Appendix A. Nomenclature

A	area (m^2) of filtration or cross section of chromatographic column
a_j	cost coefficient for a batch unit at stage j
B_i	batch size of product i (kg)
B_{ij}	batch size of product i in batch stage j (kg)
b_j	cost coefficient for a semi-continuous item associated to stage j
C	capital cost (\$)
c_j	cost coefficient for a intermediate storage tank in position j
Cap	capacity of the homogenizer (m^3/h)
D_{ij}	duty factor (size kg^{-1} h) of semi-continuous item j
F_{ij}	constant for modeling a Big-M constraint
Fd_i	fraction of released proteins denatured for product i
Fr_i	fraction of proteins released for product i
H	net available production time for all products (h)
H_i	time horizon assigned to product i (h)
k_1	rate constant for the disruption of yeast
k_2	rate constant for the denaturation of product
k_i	stoichiometric ratio of product i (kg of product/kg biomass)
M	number of batch stages in the plant
M_j	number of batch units in parallel out of phase in stage j
N_j	number of batch units in parallel in phase in stage j
Np_i	number of passes at the homogenizer for product i
P	number of products
Pr_i	production rate of product i (kg/h)
Q_i	production target (kg) of product i
R	volumetric ratio of PEG to phosphate phases
R_j	size of semi-continuous item j A (m^2) or Cap (m^3/h)
S_{ij}	size factor of product i in batch item j (size per kg)
ST_{ij}	size factor of intermediate storage tank at position j for product i (size per kg)
T	time (h)
T_{ij}	processing time of product i at batch stage j
T^0_{ij}	time factor to account for fixed amounts of time in T_{ij} (h)
T^1_{ij}	time factor to account for times proportional to B_i in T_{ij}
TL_i	limiting cycle time of product i (h)
TL_{is}	limiting cycle time of product i in subprocess s (h)
$V_{i,\,\mathrm{fer}}$	volume of fermentation broth when producing product i (m^3)
V_j	size of a batch item j (m^3)
VT_j	size of the intermediate storage tank allocated in position j (m^3)
W	volumetric ratio of diafiltration water to feed at the Microfilters
X	concentrations of biomass (kg/m^3)
y_j	binary variable that denotes the allocation of intermediate storage tank after batch stage j

Greek letters

α_j	cost exponent for a batch unit at stage j
β_j	cost exponent for a semi-continuous item associated to stage j
γ_j	cost exponent for an intermediate storage tank allocated in position j
ϕ	kinetic constant of Fermentor (per h)
η_{ij}	yield of product i at stage j
θ_{ij}	operating time of product i at semi-continuous item j (h)
Φ	maximum ratio between batch sizes of consecutive stages

Subscripts and superscripts

chr	chromatographic column
ext	extractor
fer	fermentor
hom	homogenizer
mf1	microfilter 1
mf2	microfilter 2
uf1	ultrafilter 1
uf2	ultrafilter 2
max	maximum concentration of biomass at the fermentor

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