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► **To cite this version:**

Adrian Dietz, Catherine Azzaro-Pantel, Luc Pibouleau, Serge Domenech. Ecodesign of Batch Processes: Optimal Design Strategies for Economic and Ecological Bioprocesses. *International Journal of Chemical Reactor Engineering*, 2007, 5, pp.0. hal-03594247

**HAL Id: hal-03594247**

**<https://hal.science/hal-03594247>**

Submitted on 2 Mar 2022

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# INTERNATIONAL JOURNAL OF CHEMICAL REACTOR ENGINEERING

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*Volume 5*

2007

*Article A34*

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## **Ecodesign of Batch Processes: Optimal Design Strategies for Economic and Ecological Bioprocesses**

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# Ecodesign of Batch Processes: Optimal Design Strategies for Economic and Ecological Bioprocesses

Adrian Dietz, Catherine Azzaro Pantel, Luc Guy Pibouleau, and Serge Domenech

## Abstract

This work deals with the multicriteria cost-environment design of multiproduct batch plants, where the design variables are the equipment item sizes as well as the operating conditions. The case study is a multiproduct batch plant for the production of four recombinant proteins. Given the important combinatorial aspect of the problem, the approach used consists in coupling a stochastic algorithm, indeed a Genetic Algorithm (GA) with a Discrete Event Simulator (DES). To take into account the conflicting situations that may be encountered at the earliest stage of batch plant design, i.e. compromise situations between cost and environmental consideration, a Multicriteria Genetic Algorithm (MUGA) was developed with a Pareto optimal ranking method. The results show how the methodology can be used to find a range of trade-off solutions for optimizing batch plant design.

**KEYWORDS:** multicriteria optimization, genetic algorithm, batch plant design, environmental impact

## 1. INTRODUCTION

Traditionally, system optimization in chemical and process engineering applications has focused on maximizing the economic objectives. Over the past 10 years, considerations for improving the environmental performance have started to be integrated into system optimization alongside economic criteria. These included various waste minimization approaches from the concept of mass pinch as a tool to derive cost-optimal Mass Exchange Networks with minimum emissions waste, through minimum waste water generation in process plants and waste treatments costs (Gundersen et al., 1988), to the concept of Zero Avoidable Pollution (Linninger et al., 1995). More recently, life cycle thinking (Azapagic and Clift, 1999) has started to be incorporated into the process design and optimization procedures, thus establishing a link between the environmental impacts, operation and economics of the process. In this context, this paper proposes a methodology for the integration of environmental aspect into the development process, i.e. process ecodesign that is important from both environmental and the economic perspective.

Typically the approach involves three major steps.

- (i) Process modelling and carrying out a Life Cycle Assessment study;
- (ii) Formulation of the multi-objective optimization problem in the LCA context;
- (iii) Multi-objective optimization and choice of the best compromise solution.

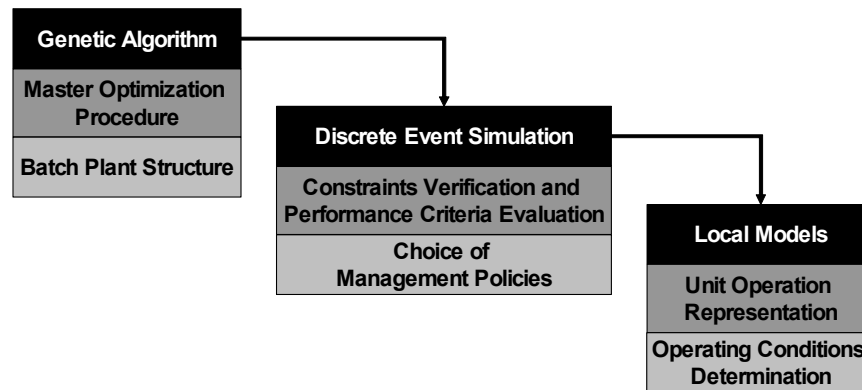
In this paper, biochemical plants are considered as an application of the proposed methodology, since they generate a wide range of liquid, solid, and gaseous waste streams that require treatment prior to discharge. The proposed work deals with the multi-criteria cost-environment design of multi-product batch plants, where the design variables are the plant configuration with equipment item sizes and parallel equipment number as well as the operating conditions. This article is organized as follows. Section 2 presents the general framework. Section 3 is devoted to the implementation of the proposed methodology. Typical results obtained on a biochemical plant are discussed in Section 4. Section 5 presents conclusions and suggests perspectives.

## 2. GENERAL FRAMEWORK

The framework for batch plant design proposed in this study (see Figure 1) integrates simple unit operation models into the batch plant wide model, which is then embedded in an outer optimization loop. The approach adopted in this work (Dietz et al., 2004) consists in coupling a stochastic algorithm, indeed a Multicriteria Genetic Algorithm (MUGA) with a Discrete Event Simulator (DES). The DES was developed using C++ object-oriented language, keeping the approach proposed in (Bérard et al., 1999). A four layer framework was proposed, resulting in the development of a standard library for the simulator classes that are general to any case, thus minimizing the task of treating different study cases or the variants of a given one (i.e. design or scheduling objectives). In this approach, at the lowest level, the common engine can be found. Most of the events at the next level are common to all batch plant simulations, but some case studies could need the definition of a particular event. Only few equipment items are common to all batch plants (i.e. storage vessels) whereas most of them are particular to each problem and

must be defined. The upper layer is the supervisor, which must be generally adapted to each study case.

The objective of the master GA involved is to propose several good and even optimal solutions, whereas the DES checks the feasibility of the proposed configuration and evaluates different criteria with both economic and ecological targets.



**Figure 1.** General methodology for optimal batch plant design

Indeed, engineering design problems are usually characterized by the presence of many conflicting objectives that the design has to fulfil. Therefore, it is natural to look at the engineering design problem as a multiobjective optimization problem (MOOP) (Bhaskar et al., 2000; Coello, 2000, Ehrgott, 2000). As most optimization problems are multiobjective by nature, there are many methods available to tackle these kinds of problems. Lately, there has been a large development of different types of multiobjective genetic algorithms, which is also reflected in the literature. The big advantage of genetic algorithms over other methods is that a GA manipulates a population of individuals. It is therefore tempting to develop a strategy in which the population captures the whole Pareto front in one single optimization run. This approach was adopted in this study.

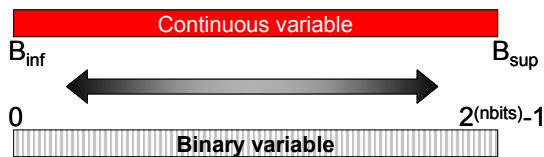
The MUGA developed in this study involves different procedures:

- A method for encoding solutions in strings of digits (or chromosomes); here, a chromosome represents a workshop configuration and the corresponding operating conditions. The encoding procedure will be briefly presented.
- An initial population has to be randomly generated.
- An evaluation function which takes a string as input and returns different fitness values which measure the quality of the solution that the chromosome represents relative to each criterion. Since this work is related to minimization cases (investment cost, limitation of pollution), the individual fitness  $F_i$  that must be maximized is calculated by:
- $F_i = C_{\max} - C_i$
- where  $C_i$  is one of the objective function value for individual  $i$ ,  $C_{\max}$  is the maximum objective function value computed on the current population for the corresponding criterion.

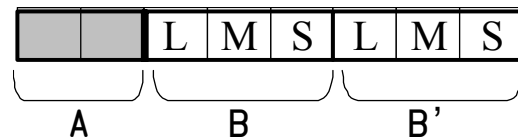
- An adaptive plan involving evolution and mutation, based on string crossover and mutation operators.

The cycle {Evaluation, Selection, Crossover and Mutation} is repeated until a stop criterion is reached. After this cycle, the Pareto sort is applied. Concerning selection and multicriteria aspects involved, it must be emphasized that for a given survival rate, the selection process is achieved via a classical Goldberg's biased roulette wheel (Goldberg, 1994), relative to each criterion. For this purpose, the initial population is randomly partitioned into sub-populations (the number of sub-populations corresponds to the number of criteria considered simultaneously). A same number of individuals is chosen for each sub-population.

A binary system was selected for encoding, as it simplifies the genetic operators, i.e., crossover and mutation. This encoding method presented was developed for the cases where the equipment items are identical at a given stage. The continuous variables were discretized and encoded in a binary way by a variable change (Figure 2), using the same bit number (i.e., eight bits). Figure 3 shows a code part used for operating stage encoding. For each stage, the equipment item number was encoded by a binary way (part A in Figure 3). The number of bits reserved to this variable set the maximum equipment item at the stage. For equipment size (L for large, M for Medium, S for Small, a number of bits equal to the available sizes for the equipment items was reserved (part B in Figure 3): the chosen size takes a positive value whereas zero is allocated to the other places. When equipment items are composed of several parts, the same approach is repeated for each component (part B and B' in Figure 3).



**Figure 2.** Continuous variables encoding



**Figure 3.** Operating stage encoding method

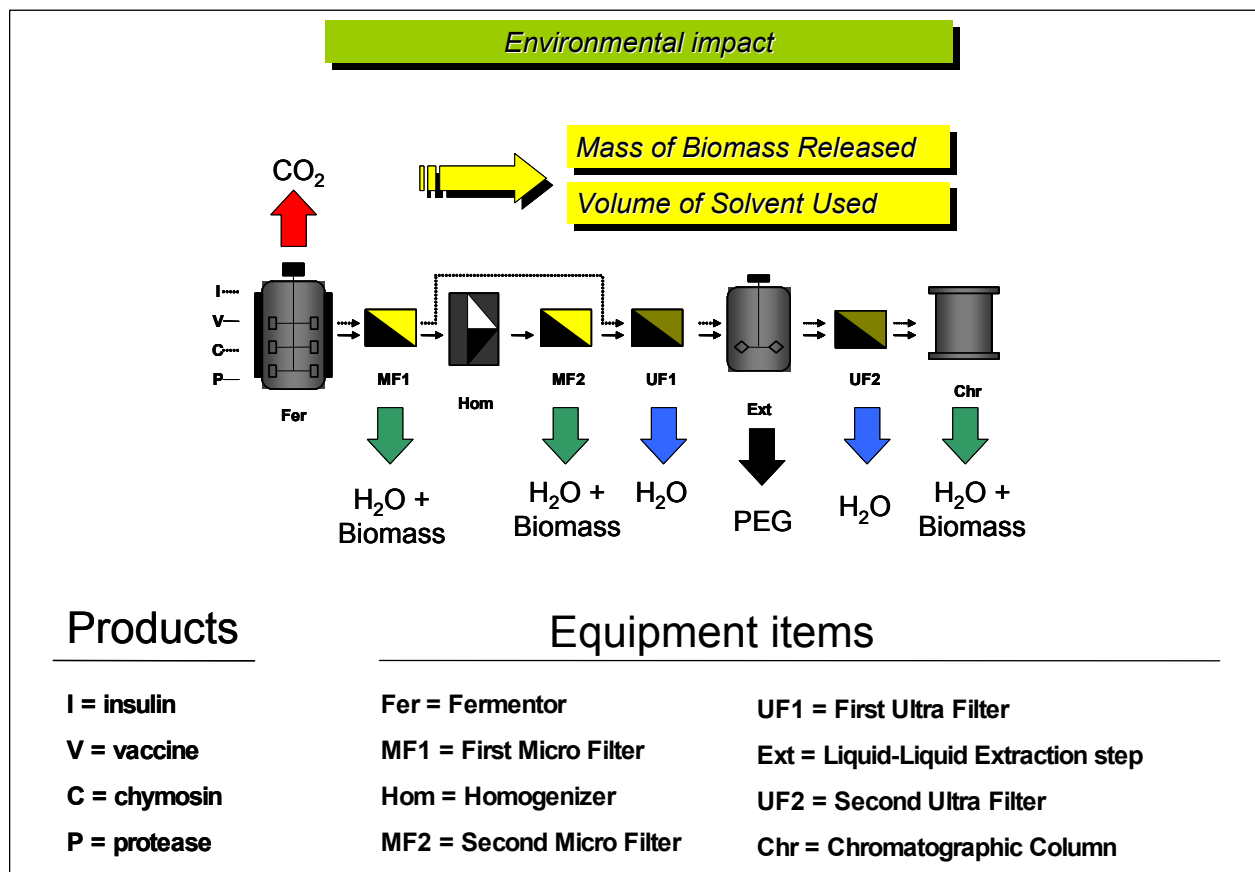
### 3. IMPLEMENTATION

#### 3.1 Presentation of the illustrative example

The previous methodology was applied to a batch plant for the production of proteins taken from the literature (Salomone et al., 1992; Montagna et al., 1994, Chiotti et al., 1996; Asenjo et al., 2000). This is a multiproduct batch plant, with four products to be manufactured by fermentation and eight treatment stages. This example is used as a test bench since short-cut models describing the unit operations involved in the process are available. The batch plant involves eight stages for producing four recombinant proteins, on one hand two therapeutic proteins, Human insulin (I) and Vaccine for Hepatitis B (V) and, on the other hand, a food grade protein, Chymosin (C) and a detergent enzyme, cryophilic protease (P). The methodology is generic for any plant producing recombinant proteins from yeast.

Figure 4 shows the flowsheet of the multiproduct batch plant considered in this study. All the proteins are produced as cells grow in the fermenter (Fer).

Vaccine and protease are considered as being intracellular, hence, for these two products, the first microfilter (Mf1) is used to concentrate the cell suspension, which is then sent to the homogenizer (Hom) for cell disruption to liberate the intracellular proteins. The second microfilter (Mf2) is used to remove the cell debris from the solution proteins.



**Figure 4.** Multiproduct batch plant for proteins

The ultrafiltration (Uf1), prior to extraction, is designed to concentrate the solution in order to minimize the extractor volume. In the liquid-liquid extractor (Ext), salt concentration (NaCl) is used to first drive the product to a poly-ethylene-glycol (PEG) phase and again into an aqueous saline solution in the back extraction.

Ultrafiltration (Uf2) is used again to concentrate the solution. The last stage is finally chromatography (Chr), during which selective binding is used to better separate the product of interest from the other proteins.

Insulin and chymosin are extracellular products. Proteins are separated from the cells in the first microfilter (Mf1), where cells and some of the supernatant liquid stay behind. To reduce the amount of valuable products lost in the retentate, extra water is added to the cell suspension.

The homogenizer (Hom) and microfilter (Mf2) for cell debris removal are not used when the product is extracellular. Nevertheless, the ultrafilter (Uf1) is necessary to concentrate the dilute solution prior to extraction. The final step of extraction (Ext), ultrafiltration (Uf2) and chromatography (Chr) are common to both the extracellular and intracellular products.

#### 4. DISCRETE EVENT SIMULATION (DES)

This section presents the DES that was developed in order to be embedded in the global framework for optimal batch plant design. The DES has two interfaces: the former with the master optimization algorithm from which it takes the batch plant configuration as well as the operating conditions, and returns the feasibility of the solution as well as the optimization criteria. The second interface links the DES with the unit operation model, the DES sends the operating conditions to the unit operation model and returns the values of the operating times as well as the results of mass balances which are then used in the criteria computation.

Following the classical terminology used in object-oriented approaches, the main so-called objects of the DES is briefly described. To treat a particular problem, specific objects should be derived from this basic structure.

The core of the simulator is the *Engine*, which has two functions: the former is to order the *Events* in its *Calendar* by their *occurrence date* whereas the latter is to activate them if the necessary resources are available; if not, it reports the Event to a next *Date*.

The *Equipment* class is a basis class for all batch plant equipment items. This class is an interface for all the objects derived from it.

An Event represents a change of the real system at a given instant. The class event is also a basis class from which the different *Events* should be defined. An *Event* is characterized by its *occurrence date*, its action over the system and a *type* that enables to give priorities when two or more *Events* have the same *occurrence date*. As a general rule, *Events* which release resources have priority over the others, and when Events have the same type, the classical FIFO rule (First In First Out) is applied.

*Product* is a basis class from which all products will derive; unlike in the previous classes, either *Event* or *Equipment*, *Product* is not an interface for its derivate classes, because it would be impossible to define an interface that takes into account all the chemical product features. To solve this issue, a particular interface class will be defined for each specific problem. The *Product* class has the name of the product and its production recipe as member data.

The *Recipe* contains the information about the treatment sequence needed to produce a specific product. Each treatment *Sequence* has as data the *treatment stage*, which contains the equipment items that can carry out the treatment, as well as the *storage stage* that contains the



equipment items that can store the *Batch* if the equipment required for the *treatment stage* is not available.

Through its member data, the supervisor has access to all the objects in the simulation and aims at supervising simulation evolution and at stopping it if given conditions are not verified.

#### 4.1 Process performance models

The process unit performance models are used to compute the operating time of each process step. A brief description of each process stage is presented in what follows and the different assumptions used to compute the processing time and the mass balance through the plant are given (for a more detailed description see (Pinto et al., 2001)). Let us note that some differences in the hypothesis were carried out because this work aims at describing the involved unit operations with simple models, in order to obtain complete information about the treatment stage (i.e. flow composition, required amount of utilities, wastes, ...). In a previous reported work (Asenjo et al., 2000), the model was only used to compute the operating time and the corresponding efficiency, with a formulation based on constraints to solve the optimization problem.

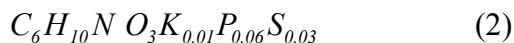
In this work, classical chemical engineering balances are carried out at each treatment stage. It must be emphasized that an additional advantage of a DES approach over mathematical programming is that different scenarios can be easily studied, for instance for scheduling or retrofitting purposes.

*Fermentor.* A logistic kinetic expression, constrained by a limiting biomass concentration, is assumed for cell growth:

$$\frac{dX_{i,fer}}{dt} = \varphi_i \cdot X_{i,fer} \left( 1 - \frac{X_{i,fer}}{X_{i,max}} \right) \quad (1)$$

The same constant kinetic,  $\varphi_i = 0.26 \text{ h}^{-1}$  is estimated for all the products, as well as the following maximum biomass concentration  $X_{i,max} = 55 \text{ Kg/m}^3$ .

The global equivalent elementary composition of the cells is (Serra, 2004):



In the following, the contributions of K, P and S are neglected.

The calculation of the protein ratio in the cell is carried out from a classical empirical formula such as:

$$X_p^{tot} = 6.25 \cdot X_{N_2} \quad (3)$$

The ratio of the interest product in the cell is computed by:

$$X_i = k_i \cdot X_p^{tot} \quad (4)$$

It is assumed that 40% of biomass is composed of proteins; and  $k_i$  is a ratio (kg of product  $i$  / kg total de proteins) estimated as 0.05; 0.1; 0.15 and 0.2 for insulin, vaccine, chymosin, and protease, respectively.

By integrating equation (1) between an initial biomass concentration of 5% of the maximal biomass concentration  $X_{i,max}$  and the fermentor final concentration  $X_{i,fer}$ , with adding a downtime of 4 h, the fermentation time is then obtained.

*First microfilter.* This stage consists of three items: a batch retentate holding vessel, the microfilter itself and a permeate holding vessel, used only by extracellular proteins.

For intracellular products, the aim of this stage is to reduce the batch size, which is of major importance in order to reduce the size of the following stages. For the extracellular products, the proteins are separated from the cells and water is added to avoid product loss.

The time required to perform the filtration is proportional to the permeate volume, inversely proportional to the membrane surface and also proportional to the membrane permeability.

*Homogenizer.* The vaccine and protease batches proceed through the homogenizer for cell disruption. The homogenizer time is proportional to the volume feed, and inversely proportional to the homogenizer capacity. The volume fed to the homogenizer is the batch volume time the number of passes through the homogenizer.

Successive passes through the homogenizer drive the fraction cell disrupted asymptotically to 1, which is also the fraction of proteins released. The same approach is valid to estimate the fraction of proteins released that are denatured by the homogenizer.

*Second microfilter.* Cell debris is separated from vaccine and protease at this stage. Filtration is limited to 50% reduction in the retentate initial volume to avoid operational problem due to the large concentration of solid matter. Then, water is added, as in the first microfilter stage for extracellular proteins to avoid product loss.

*First ultrafilter.* The purpose of this stage is to remove water up to a limit of total protein concentration, estimated as  $50 \text{ kg/m}^3$ , in order to reduce as much as possible the size requirement of the downstream stages while still avoiding the risk of protein precipitation as NaCl is added to the extractor.

*Liquid-liquid Extraction step.* The decision variable at this stage is the volumetric ration of poly-ethylene-glycol PEG to phosphate phase,  $R_i$ . Back extraction is assumed to be conducted with an aqueous phase volume identical to the feed volume, thus obtaining the maximum dilution if NaCl that is compatible with the use of the same vessel for the consecutive extraction and back extraction.

The extraction-back extraction model used is a simplification of the rigorous model. The kinetics for both mixing and phase separation was simplified by assuming that these stages are completely achieved after five minutes of mixing and 30 minutes of settling. Adding 10 minutes

for each charge or discharge and considering the sequence of eight operations (charge-mixing-settling-discharge of the phosphate phase-charge of the fresh phosphate phase-mixing-settling-discharge) leads to a constant time of 1.8 h.

*Second ultrafilter.* The purpose of this stage is simply to raise again the concentration of total proteins to  $50 \text{ kg/m}^3$ .

*Chromatographic column.* It is assumed that the chromatographic column works at a constant velocity of 4 m/h and that its pack binding has a capacity of  $20 \text{ kg/m}^3$ . A 50% capacity of the maximum capacity is used so as to avoid excessive product breakthrough.

A column height of 0.5 m was assumed, which is large enough to allow high resolution and is still compatible with reasonable linear velocities.

Elution plus washing-regeneration solution volumes were assumed to reach three times the column volume, and the linear velocity for this process to be the same as for loading.

The economic and ecological impact of all process variables will not be analyzed in detail. Let us only consider the ratio of washing water at microfilter 2. For the sake of illustration, the operation yield is plotted vs. the washing water ratio. The influence of the process variable is clearly shown, since an increase in the amount of water increases the operation yield. This would also result in an increase of the size of both microfilter 2 and size of ultrafilter 1 (this steps aims at re-concentrating the diluted protein solution), and consequently in an increase in equipment cost for these two items.

## 4.2 Simulation results and discussion

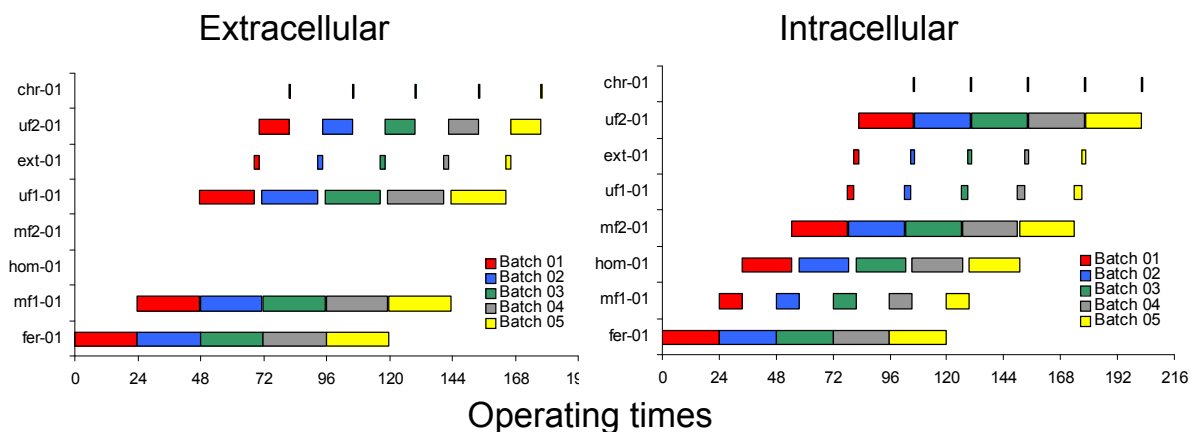
The unit operation performance models have then been embedded in the DES model to determine the behaviour of the plant. In this section, some results of simulations are presented to give an idea of the potential of the simulator, which is particularly interesting for reducing the costly and time consuming process setups.

Let us recall that (Pinto et al., 2001) only used a monocriterion optimization approach based on investment cost for batch plant design with equipment sizes and operating conditions as variables, under several intermediate storage policies.

In (Montagna et al., 2000) and (Asenjo et al., 2000), a strategy based on monoprodut campaigns was assumed, even when considering the design of a multiprodut batch plant.

Two preliminary simulation runs were performed in order to validate our approach on the example treated by (Pinto et al., 2001).

In both simulations (Figure 5), the process operating conditions were taken from (Montagna et al., 2000), with constant time and size factors; the equipment number corresponds to the solutions obtained in the different cases of optimization. The plant was composed of one equipment item for each stage of treatment and a policy of no intermediate storage was applied. The equipment size was fixed in order to guarantee a high use rate.



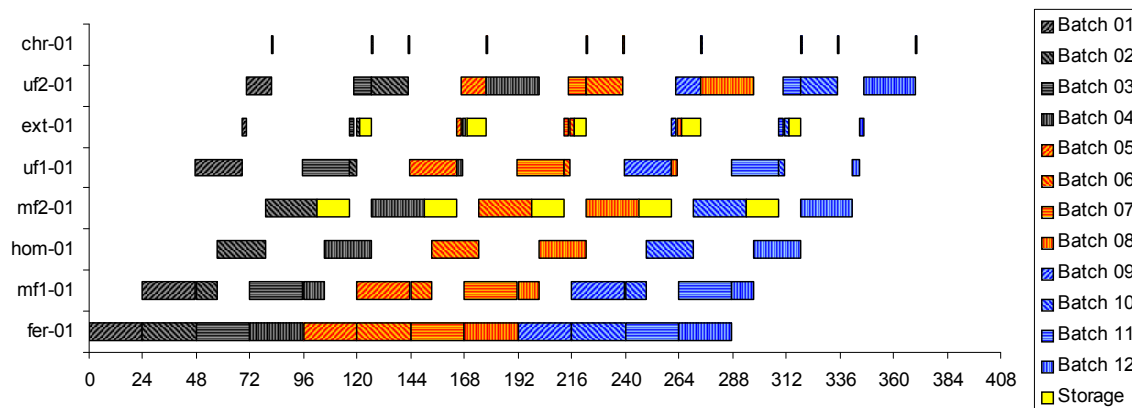
**Figure 5.** Simulation results for the monoprodukt campaign policy

Let us note that the conditions of the optimal solutions found by these authors have not yet been exactly reproduced since the assumptions on mass balance are not the same. More precisely, they only take into account the interest proteins, while all the compounds of a given batch must be considered to estimate the environmental impact at the design stage.

In Figure 5, the temporal sequence of the various procedures and their operations can be visualized in detail through the operations Gantt chart relative to extra- and intracellular protein products for five monoprodukt campaigns. Since the fermentation step is the longest operation, the campaigns start when a fermentor is available. At this stage, some remarks can be pointed out: when an extracellular product is processed, there are two equipment items that are not used (hom-01 and mf2-01), because cells do not need be disrupted to extract the product. In the case of intracellular products, it can be observed that the first microfilter used for extracellular proteins has an acceptable utilisation rate. The non-use of additional water at this stage for intracellular products reflects this important difference. A similar behaviour is observed for the first ultrafiltration stage. In this case, the analysis of process modelling reveals that intracellular products arrive after two microfiltration stages, instead of one for extracellular products. Thus, the concentration is higher and, consequently, the amount of water to be filtered takes a lower value.

Let us note that the liquid-liquid extractor has a very low use rate. This stage has a constant operation time of 1.8 h, which is very small in comparison with the other stages, i.e., the fermentation time is around 24 h. and can not be improved in any way.

Another alternative using multiprodukt campaigns was tested in this study (see Figure 6). This kind of strategy can be directly tested by using the DES while its implementation needs another formulation when using mathematical programming techniques.



**Figure 6.** Simulation results for the multiproduct campaign policy

While keeping the same batch plant structure, we propose a multiproduct campaign with a batch of each product to be produced. The starting order of the different batches was fixed altering intracellular and extracellular products. The first remark is that the same batch plant was able to produce the same production rate in both operating modes. In the multiproduct campaign, only an additional assumption has been made concerning the possibility for a batch to stay in the active process step for storage (unavailability of storage vessels or of the following process steps).

It can also be observed that the equipment items which present a low use rate for some products in the previous plant operating mode, have now a regular use rate. In turn, now, four of the eight stages are oversized around 100%.

The approach based on the coupling of a DES with unit operation models shows its flexibility since no modification in the model formulation is required. Thus, different strategies can be directly tested for sensitivity analysis and could be thus automatically treated when embedded in the global optimization tool. More precisely, the parameters are campaign composition, number of products per campaign, number of batches of each product, batch sizes, starting order of the campaign batches and the time interval between campaigns.

## 5. ENVIRONMENTAL IMPACT EVALUATION

Several methodologies for environmental impact (EI) consideration are available in the literature. The most important concept refers perhaps to the Life Cycle Assessment (LCA) (Burgess and Brennan, 1999) considering all the wastes generated in order to produce the different products in the upstream stages (i.e., raw material production, energy generation, etc.), in the study stage (i.e. solvents, non-valuable by-products, etc) and in the downstream steps (i.e. recycling, incineration, etc). The aim of LCA is to consider the wide chain in order to prevent pollution generation and to compare the different alternatives to produce a product. Another concept used the Pollution Balance (PB) principle to carry out a pollution balance (Cabezas et al., 1999) equivalent to the balance made for mass or energy. It means that a process can not only pollute but also consume a polluting product and will be a benign process.

Finally, the Pollution Vector (PV) methodology (Stefanis et al., 1995) consists in evaluating the environmental impact by means of an impact vector over different environments (i.e. water, air, etc) defined as the mass emitted on an environment divided by the standard limit value in this environment.

Given the production recipes for the different products and the general flow-sheet, the first step consists in applying the LCA methodology to determine all the products contributing to the environmental impact (Figure 4). For information availability reasons, the study was reduced to the process being studied, which is of course a limited application of LCA. Products (i.e. vaccine) and raw materials (glucose, NH<sub>3</sub>) were considered not having an environmental impact. After that, a PB is applied, using the PV to quantify the environmental impact. In this case, an adapted definition of the pollution vector was introduced, because the standard limit values for the polluting product were not found in the literature. This vector has two components; the former is the total biomass quantity released and the latter concerns the PEG volume used. Even if the solvent can be recycled, it cannot be carried out at 100%, so the environmental impact is considered to be proportional to this quantity. The pollution indexes were thus defined as the emitted quantities divided by the mass of the manufactured products. Let us remark that the environmental impact minimization can be viewed a multicriteria problem in itself.

The global index of each environmental impact criterion is defined as a weighted sum with respect to the production of each product index (eq. 5).

$$I_k = \frac{I_k^{ins} \cdot P_{ins} + I_k^v \cdot P_{vac} + I_k^{chy} \cdot P_{chy} + I_k^{pro} \cdot P_{pro}}{P_{ins} + P_{vac} + P_{chy} + P_{pro}} \quad (5)$$

where  $I_k$  is the pollution global index,  $I_k^i$  is the  $k$  pollution index of  $i$  product defined as the kilograms of the pollutant  $k$  by kilograms of manufactured product  $i$  and  $P_i$  is the total production the  $i$  product.

The cost criterion considered in this study is classically based on investment minimization because there was not enough information to evaluate the operational cost of the batch plant (raw material cost, utilities cost ...) and to embed it in a net present worth computation.

The optimization criterion involving investment cost for equipment and storage vessels  $I_{Cost}$  is calculated using (6):

$$I_{Cost} = \sum_{i=1}^{N_{OP}} \sum_{j=1}^{N_{EQ^i}} \left( A_i + B_i V_{ij}^{C_i} \right) + \sum_{k=1}^{N_{SV}} \left( A_k + B_k V_{sk}^{C_s} \right) \quad (6)$$

where  $N_{OP}$  is the number of operations,  $N_{EQ}$  is the number of equipment items (for operation  $i$ ),  $N_{SV}$  is the number of storage vessels,  $A_i$ ,  $B_i$  and  $C_i$  are the cost coefficients for operation  $i$  or storage vessels,  $V_{ij}$  (respectively  $V_{sk}$ ) is the volume of equipment  $ij$  (respectively of storage vessel  $k$ ).

Concerning the definitions of the criteria, it must be pointed out that they were selected for illustration purposes. However, since the economic criterion is only based on investment cost, the biomass loss may be considered as only an environmental deficit. In a case where larger quantity of solvent is needed and the product(s) is (are) of higher added value, a decision of less solvent usage and with larger loss of biomass could be favoured by the method presented here. This is misleading because the economic loss due to the biomass loss has been much lower estimated.

The models representing the operation units involved in the global process are presented in detail in (Dietz et al., 2005) and will not be recalled here.

The optimization problem considered can be formulated as follows:

$$\begin{aligned} \min f_1(y) \\ \min f_2(x) \\ \text{s.t. } g(x,y) \leq H \end{aligned}$$

where  $f_1$  represents the investment cost and  $f_2$  the environmental impact. The  $x$  vector represents the operating conditions and refers to batch plant configuration.

Without going into further detail, the optimization problem involves 44 variables, which may be either continuous (i.e. the operating conditions) or discrete (parallel equipment number, equipment size).

A set of data must be fixed by the user concerning the optimization problem definition before the implementation of the design methodology (see Dietz et al., 2005). For instance, the annual demand for each product is presented in Table 1.

**Table 1.** Product demands

Product	Production (kg/year)
Insulin	1500
Vaccine	1000
Chymosin	3000
Protease	6000

Three sizes are available for each equipment item: large (L), medium (M) and small (S). The classical expressions used for computing the investment cost of the equipment items follows a classical scaling law. Of course, a thorough economic study would also include the operating cost estimation and analysis of profitability. Since this kind of analysis only requires reliable economic data for a real process and does not induce additional difficulties in the chosen resolution strategy, a capital cost-based study was finally adopted for the preliminary economic evaluation of the project for manufacturing biological products.

## 6. RESULTS AND DISCUSSION

From the simulation results presented in the previous section, two production policies were kept, i.e., mono and multiproduct for optimal batch plant design purposes. In the case of a mono product production policy, all the batches of a product are manufactured before treating a batch of another product. The products are manufactured alternating intra and extra cellular product, the order is as follows: insulin, vaccine, chymosin and protease. The multiproduct production policy the production is carried out manufacturing alternating one batch of each product in the above mentioned order.

Table 2 presents the available range in terms of size for each equipment type and Table 3 proposes the classical expressions used for computing the investment cost of the equipment items, following a classical scaling law.

**Table 2.** Available equipment item sizes

<b>Equipment item</b>	<b>Large</b>	<b>Middle</b>	<b>Small</b>
Fermenter [m <sup>3</sup> ]	6	3	1
First micro filter – retentate vessel [m <sup>3</sup> ]	6	3	1
First micro filter – filtration surface [m <sup>2</sup> ]	5	2.5	1
First micro filter – permeate vessel [m <sup>3</sup> ]	6	3	1
Homogenizer – holding vessel [m <sup>3</sup> ]	6	3	1
Homogenizer – capacity [m <sup>3</sup> /h]	0.5	0.25	0.1
Second micro filter – retentate vessel [m <sup>3</sup> ]	6	3	1
Second micro filter – filtration surface [m <sup>2</sup> ]	5	2.5	1
Second micro filter – permeate vessel [m <sup>3</sup> ]	6	3	1
First ultra filter – filtration surface [m <sup>2</sup> ]	50	25	10
First ultra filter – permeate vessel [m <sup>3</sup> ]	6	3	1
Liquid – Liquid extractor	6	3	1
Second ultra filter – permeate vessel [m <sup>3</sup> ]	6	3	1
Second ultra filter – filtration surface [m <sup>2</sup> ]	5	2.5	1
Chromatographic separation – holding vessel	6	3	1
Chromatographic separation – column	1	0.5	0.25
Storage vessel	6	3	1

Table 4 displays the parameters of the genetic algorithm used for multicriteria batch plant design. In this work, the generation number was fixed as twice the population size. The global survival rate is relatively low as compared to standard values for optimization of test mathematical functions (Dedieu et al., 2003). Moreover, a high mutation rate was set. Although a systematic study was not carried out to find these values, they were chosen from several preliminary tests and agree with previous works (Dedieu et al., 2003) where similar problems were treated. The elitism was used in order to avoid losing the best solution for each criterion. Considering the stochastic aspect of GAs, several optimization runs were carried out for each multicriteria optimization. Given that solutions obtained in one optimization run could be dominated by solution of another one, a Pareto sort procedure is applied to the set of solutions



obtained at each optimization run, and the non-dominated solutions are considered as the solutions proposed by the methodology.

**Table 3.** Cost coefficients

UNIT	Size	Cost
Fermenter	$V_j$ (m <sup>3</sup> )	$63400.V^{0,6}$
micro- and ultrafilter	Vretentate (m <sup>3</sup> )	$5750.V^{0,6}$
	Vpermeate (m <sup>3</sup> )	$5750.V^{0,6}$
	Afilter (m <sup>2</sup> )	$2900.A^{0,85}$
Homogenizer	Vholding (m <sup>3</sup> )	$5750.V^{0,6}$
	Cap (m <sup>3</sup> /h)	$12100.cap^{0,75}$
Extractor	Vextr (m <sup>3</sup> )	$23100.V^{0,65}$
	Vholding (m <sup>3</sup> )	$5750.V^{0,6}$
Chromatography Column	Vchrom (m <sup>3</sup> )	$360000.V^{0,995}$

In previous works (Dietz et al. 2005), the approach using a MOGA was applied to the same example for monocriterion batch design. The monocriterion results were presented and analyzed in detail Dietz et al. (2005). In this work, the best solutions obtained for each criterion are used to evaluate the performance of the MUGA.

**Table 4.** Genetic algorithm parameters

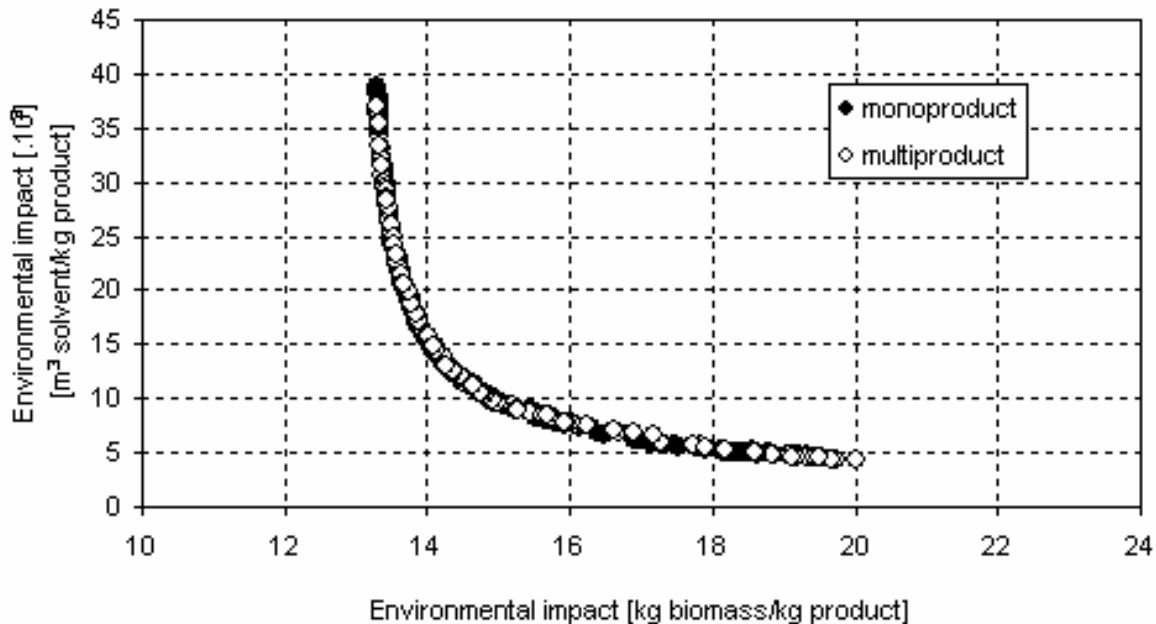
	Bicriteria Solvent-biomass	Bicriteria Cost-Solvent	Bicriteria Cost-Biomass	Tricriteria Cost-EI
Population size	300	450	450	600
Generation number	600	900	900	1200
Survival rate	0.5	0.5	0.5	0.5
Mutation rate	0.4	0.4	0.4	0.4
Elitism by criterion	1	1	1	1

The MUGA presented in this work was first used to demonstrate that the two EI criteria considered that are respectively the total biomass quantity and the PEG volume, present antagonist goals (Figure 7). Very similar results were obtained at each optimization run, so only the results after the final Pareto sort procedure are presented in Figure 7. Moreover, it must be noted that slight differences are obtained between both production policies because the environmental impact depends only on the mass balance that is function of the continuous variables.

This antagonist behaviour can be explained at the liquid-liquid extraction stage. The more solvent is used, the more efficient the stage becomes and, consequently, the fewer products are

lost, reducing the environmental impact index computed as Kg of biomass released by kg of final product.

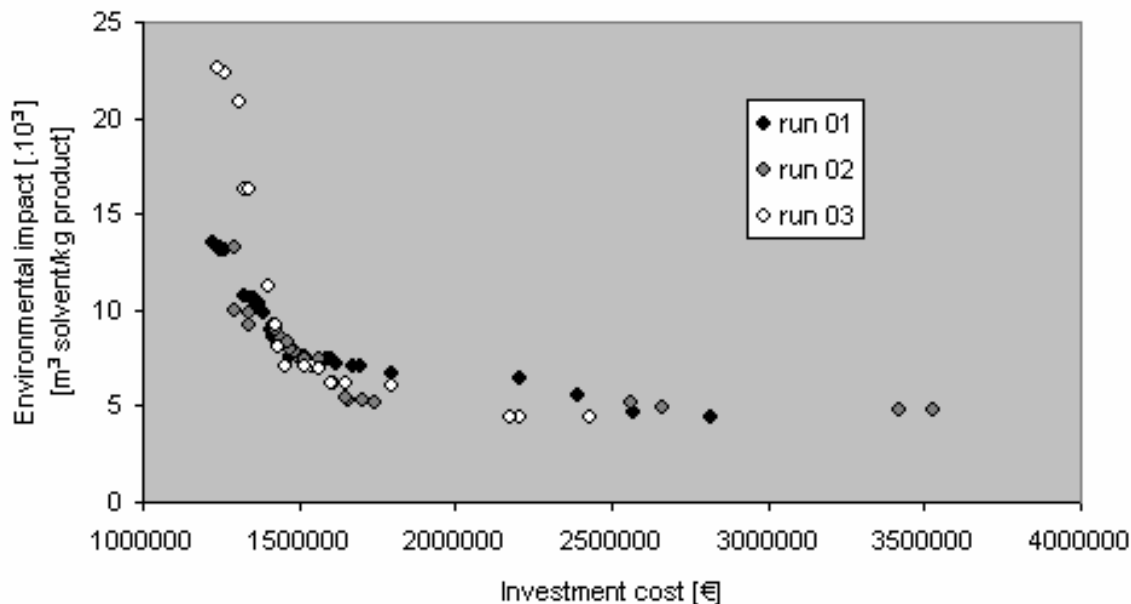
The same approach was also applied to the cost – environment criteria. First, the amount of solvent used and the investment cost were considered.



**Figure 7.** Pareto's optimal solutions for biomass released-solvent amount criteria (bicriteria case)

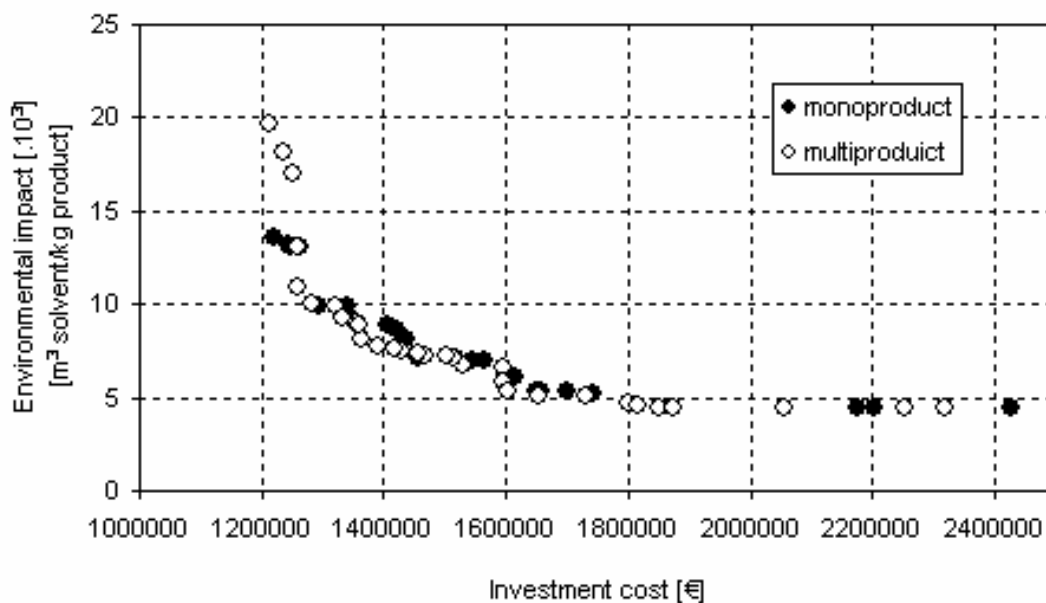
For illustration purposes, Figure 8 shows the results obtained at each optimization run for the monoproduct production policy, performed with an identical parameter set to guarantee the stochastic nature of the GA. In this case the results are not superposed as it was the case for the bicriteria optimization biomass – solvent, which show the need of carrying out several optimization runs for the same problem.

In Figure 8, it can be seen that each optimization run is oriented to a part of the search region. The first optimization comes up with the better solution for the cost criterion, the second for the environmental criterion and the third is a compromise between both. The final Pareto sort procedure is carried out over these solutions. The final results for both production policies are presented in Figure 9. Let us note that the Pareto zone is constituted of sparse points, since the adaptation function related to the investment cost takes discrete values.



**Figure 8.** Pareto's optimal solutions for solvent used-investment cost (bicriteria case)

Slight differences were found between both production policies. The antagonist behaviour between these two criteria, investment cost – amount of solvent used, can be explained by a compromise between the solvent yield and the process global yield. When process yield is penalized, a bigger, and consequently more expensive, batch plant is required.



**Figure 9.** Pareto's optimal solutions for solvent used-investment cost (bicriteria case)

In order to evaluate the search performance of the GA, table 5 presents the best solution that is obtained at each optimization run for each criterion considered as well as the best solution obtained with a monocriterion approach. Even though the methodology was not able to find the best solution, the values exhibit the same order of magnitude (around 5% more expensive for the investment cost criterion). It must be noted that in the monocriterion optimization (see Dietz et al. (2005)), the best value was obtained only once and, in the other cases, the solutions were around 2%-3% more expensive, which justifies the results when several criteria are taken into account simultaneously. The number of solutions obtained in each optimization run was around of 25. It is important to note that in each case, the solutions are uniformly distributed in the search space; this means that there is no preferential search region in the multicriteria search as shown in Figure 8.

**Table 5.** Bicriteria Cost-Solvent optimization results

	Monoproduct			Multiproduct		
	Cost	Solvent [10 <sup>3</sup> ]	Solutions	Cost	Solvent [10 <sup>3</sup> ]	Solutions
Run 1	1221890	4.445	32	1303730	5.070	21
Run 2	1290490	4.779	23	1211100	5.006	28
Run 3	1238050	4.415	23	1257200	4.406	23
Best	1140990	4.386	---	1139100	4.386	---

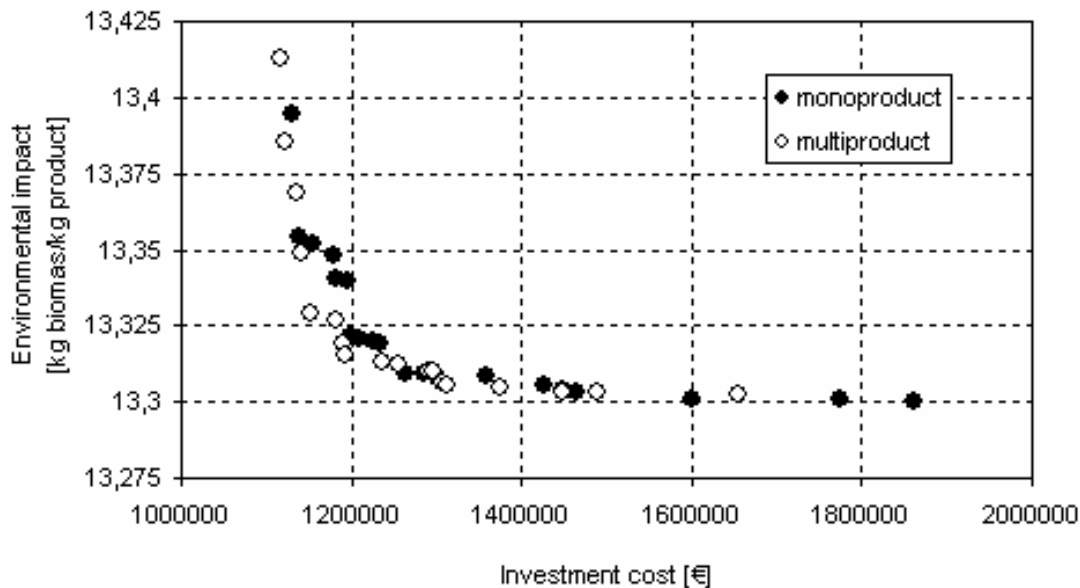
It is also interesting to see where the results are positioned with respect to the non-considered criterion, in this case the amount of biomass released. Table 6 presents the range of values for this criterion for both production policies, which present the same order of magnitude.

Moreover, the minimal value of the range is close to the best value obtained in monocriterion optimization (see table 5) value which allows to predict less antagonism between investment cost and biomass released criteria.

**Table 6.** Values range for the other criterion

	Biomass for Cost-Solvent		Solvent for Cost-Biomass	
	Minimum	Maximum	Minimum	Maximum
Monoproduct	14.393	20.369	36.03 10 <sup>-3</sup>	40.58 10 <sup>-3</sup>
Multiproduct	14.261	22.889	34.9 .10 <sup>-3</sup>	41.88 10 <sup>-3</sup>

The last bicriteria optimization considers the investment cost and biomass released. As for the previous case, three optimization runs were carried out for each production policy. The results obtained after the final Pareto sort procedure are presented in Figure 10 and are similar for both production policies as it was shown for the cost-solvent criteria.



**Figure 10.** Pareto's optimal solutions for biomass released-investment cost (bicriteria case)

Table 7 presents the best solution obtained at each optimization run for each criterion considered as well as the best solution obtained with a monocriterion approach. As for the criterion referring to the amount of biomass released, the best value is obtained at each optimization run, as it was the case for the amount of solvent in the previous bicriteria optimization. The number of solutions is slightly inferior to the previous results. This can be explained by the lower antagonism between the biomass and the cost criteria. A better solution than the one of the MOGA (only 2% better) was found again for both production policies. This shows the drawback of the stochastic optimization methods because they can not guarantee the solution optimality. Besides, it must be noted that the GA parameters were not the same. In the case of the MUGA, a larger population was used, but at the same time it must be noted that the fact that several criteria were taken into account is not penalizing in the GA. The environmental impact criteria guide the search of batch plants with several equipment items diversifying the search paths.

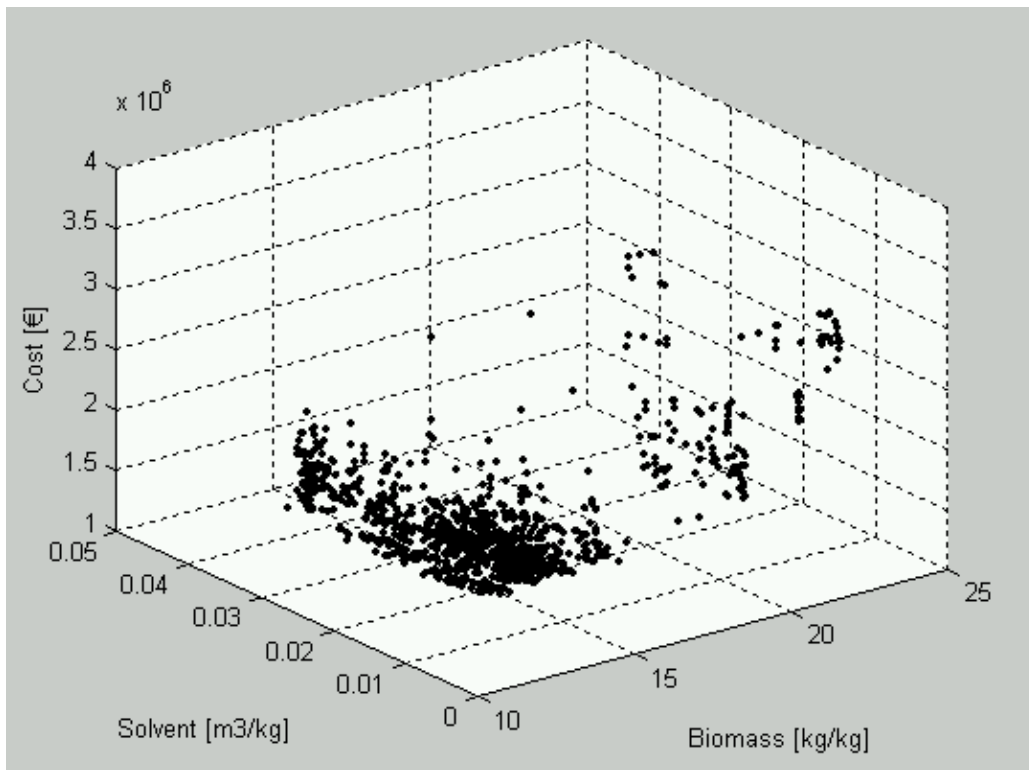
**Table 7.** Bicriteria Cost-Biomass optimization results

	Monoproduct			Multiproduct		
	Cost	Biomass	Solutions	Cost	Biomass	Solutions
Run 1	1143080	13.303	10	1252280	13.307	15
Run 2	1235340	13.300	10	1289530	13.303	13
Run 3	1129290	13.305	15	1116950	13.302	22
Best	1140990	13.299	---	1139100	13.305	---

Table 6 presents the range of values for the non-considered criteria, the amount of solvent used. These values are distant from the best values, which reminds the antagonism of this criterion, with respect to the other considered as objective functions.

The results obtained show the typical compromise between cost and each environmental index. Since the conflicting behaviour between each pair of criteria (investment cost, solvent used and biomass released) was demonstrated, the final multicriteria cost-environment batch plant design was carried out, keeping the two environmental criteria independent: this simply means that the same survival rate was considered for each criterion.

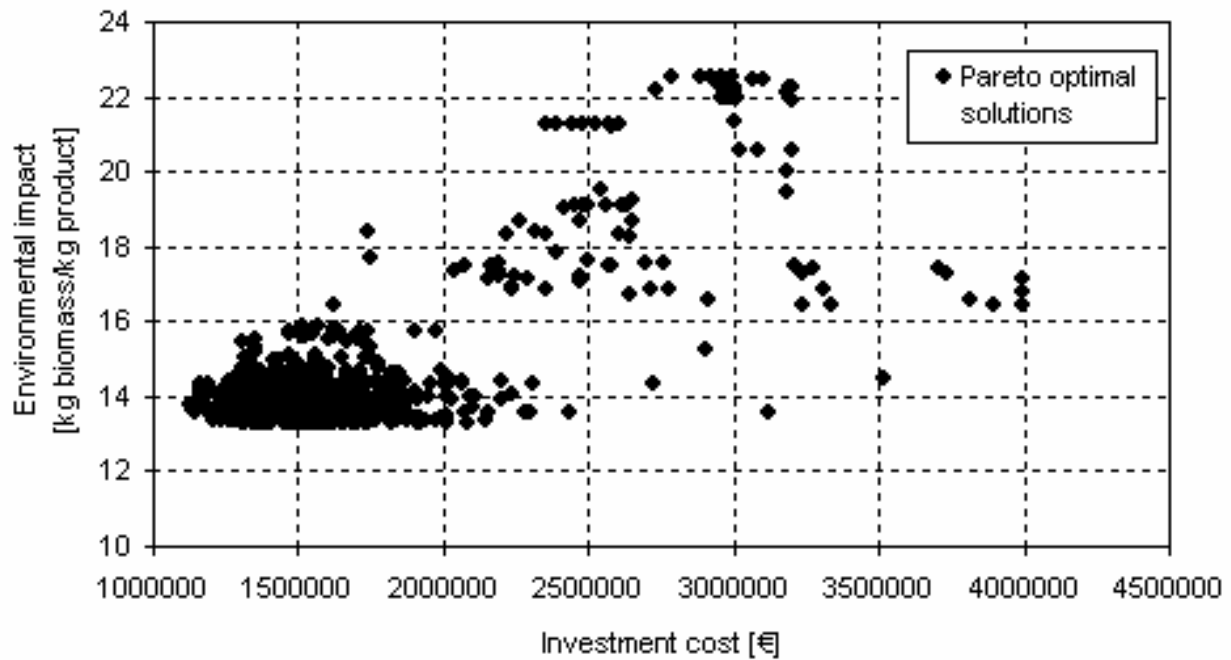
As previously, three optimization runs were carried out for each production policy. Given the similarity of the results with both production policies (see table 5 and 7), only the results obtained with a multiproduct production policy are presented (Figure 11).



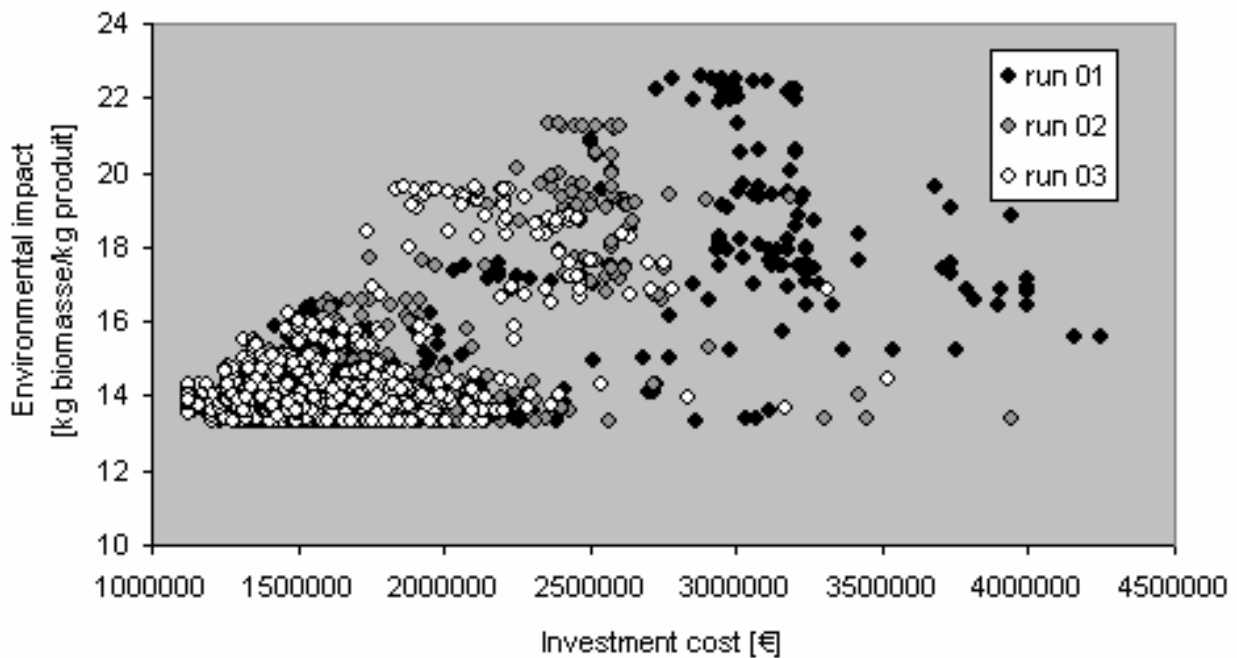
**Figure 11.** Pareto's optimal solutions Cost – IE (tricriteria case)

To facilitate result interpretation, a projection over the plane of interest (relative to two given criteria) was carried out (Figures 12 to 16). It can be observed that most solutions referring to the previous bi-criteria optimization are found again. In all three cases, the points are more concentrated near the compromise zone, which is interesting for final decision. In order to evaluate the methodology, Figures 12, 14 and 16 show the results projected for each optimization run. In this case, it can be observed that several optimization runs are necessary, given the complexity of considering a third criterion; the results are not systematically superposed as for

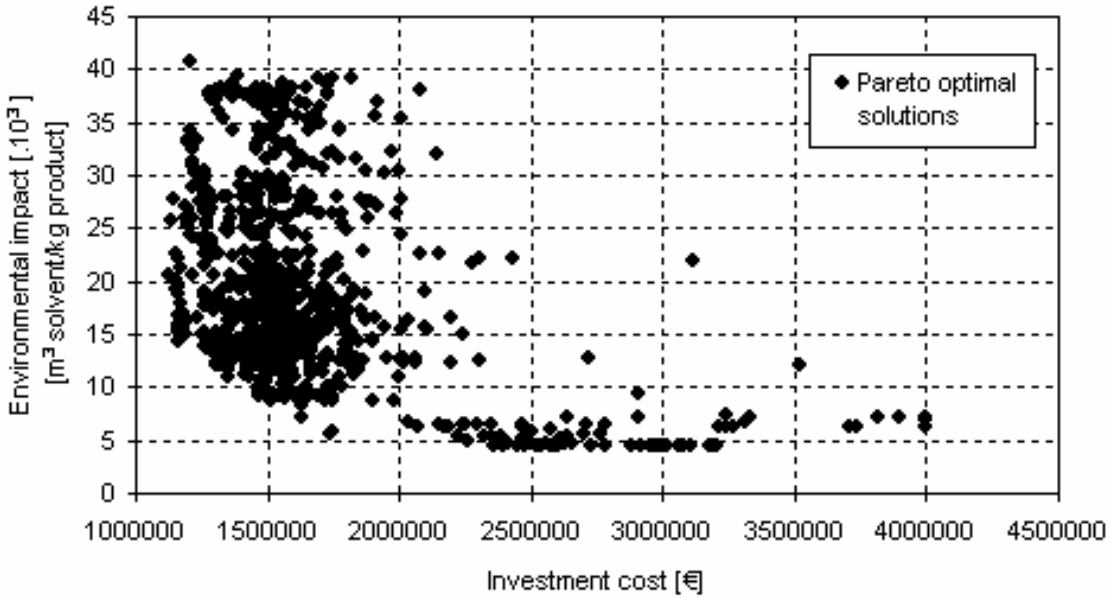
the bicriteria case study. Two options could be suggested for improvement, i.e., larger population and generation number as well as some extra optimization runs.



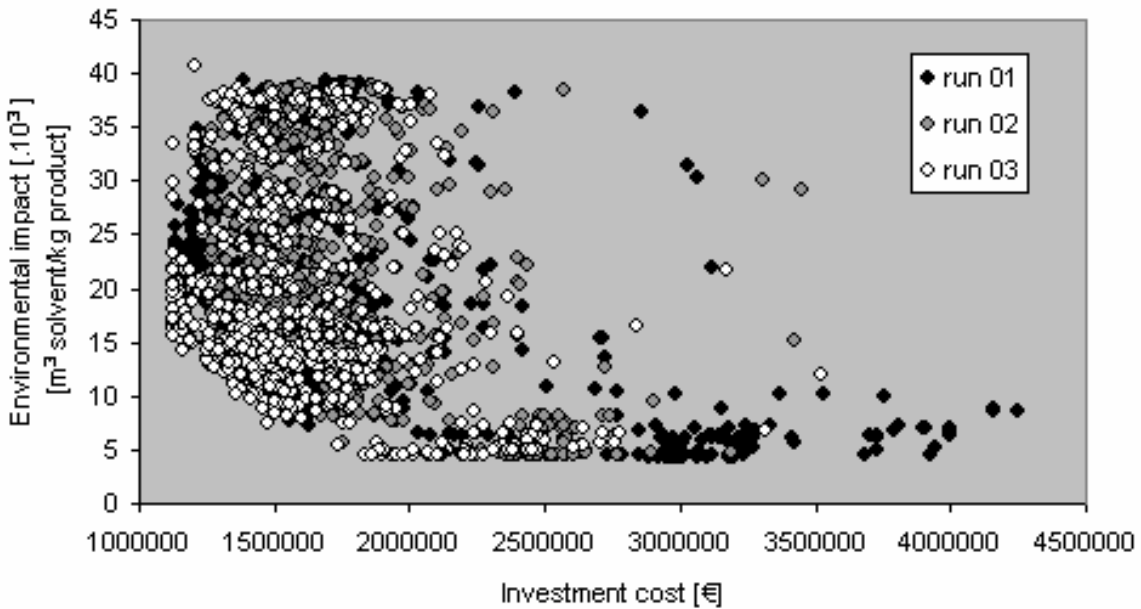
**Figure 12.** Pareto's optimal solutions Cost – Biomass (tricriteria case)



**Figure 13.** Pareto's optimal solutions Cost – Biomass (different optimization runs)

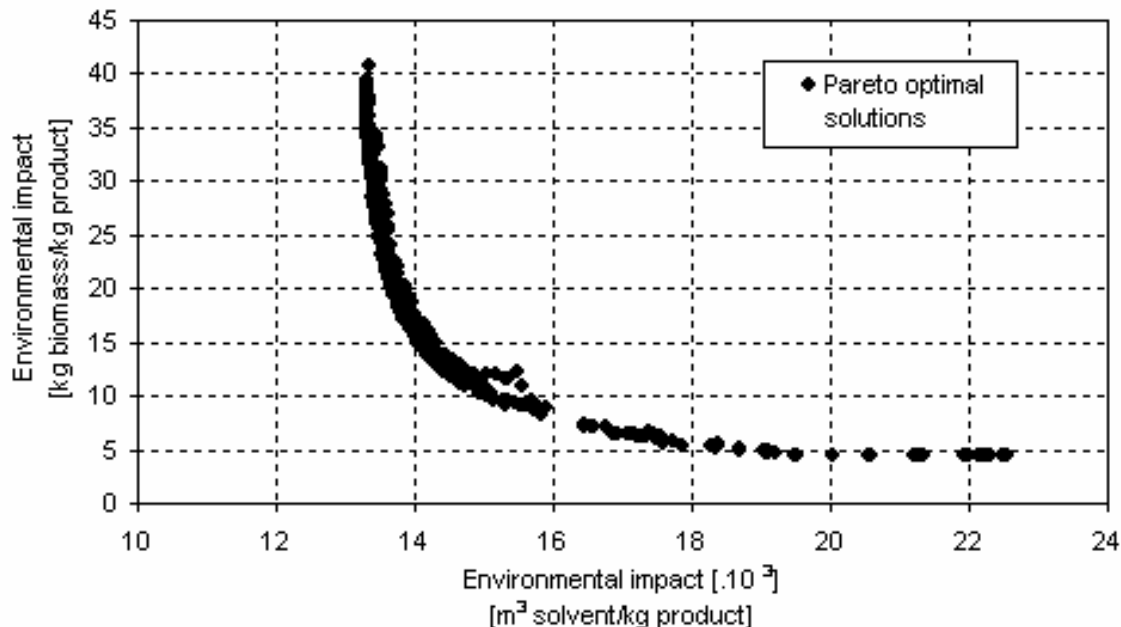


**Figure 14.** Pareto's optimal solutions Cost – Solvent (tricriteria case)



**Figure 15.** Pareto's optimal solutions Cost – Solvent (different optimization runs)





**Figure 16.** Pareto's optimal solutions Cost – Solvent (tricriteria case)

Table 8 presents the best solution for each criterion for both production policies. As it was mentioned, there are only slight differences between both production policies. It also shows that the monocriterion search is not penalized by the multicriteria one. In other words, the same GA is able to carry out both, even when several antagonist objective functions are considered.

**Table 8.** Multicriteria cost-environmental impact results

	Monoproduct			Multiproduct		
	Cost	Solvent [10 <sup>3</sup> ]	Biomass	Cost	Solvent [10 <sup>3</sup> ]	Biomass
<b>Run 1</b>	1232630	4.438	13.303	1130860	4.393	13.300
<b>Run 2</b>	1207900	4.421	13.304	1265100	4.447	13.303
<b>Run 3</b>	1279110	4.391	13.304	1124630	4.459	13.301

## 5. CONCLUSIONS

A methodology was proposed for batch plant design, considering both investment cost and environmental impact minimization. An optimization scheme has been implemented using a multiobjective genetic algorithm with a Pareto optimal ranking method. This technique is ideally suited to this type of problem, where a number of conflicting considerations must be taken into account. The use of MUGA makes possible a robust optimization technique, across a non-linear search space (the objective functions are computed by the use of a discrete event simulator

(DES) integrating shortcut unit operations models) linking multiple variables and objectives. The paper clearly shows that opportunities for process optimization and environmental impact minimization must be considered at the early stages of process development before the process is frozen due to regulatory reasons.

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