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Many-objective optimization of a three-echelon supply chain: A case study in the pharmaceutical industry☆

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ABSTRACT

This paper proposes an order-up-to (OUT) replenishment policy integrated with inventory routing optimization, formulated as a three-echelon supply chain. The OUT policy is used for raw material purchasing and transportation from the suppliers to support warehouses. Inventory routing optimization is applied to transport the raw materials to the main warehouse when required, where manufacturing operations take place. The optimization problem is solved using a many-objective genetic algorithm. The proposed optimization framework can be applied to the pharmaceutical industry and to any other highly dynamic industry with large product portfolios. This paper presents a real-world case in the pharmaceutical industry from Hovione Farmaciência SA. The performance of the many-objective optimization is compared with a summed single-objective simplification, showing that while the total cost reduces by using single-objective optimization, the optimal scenarios offered by the many-objective optimization may provide additional insight to decision-makers and act as a decision support system, being more inline with the human–machine cooperation trends of the industry.

1. Introduction

With the Industry 4.0 becoming more commonplace throughout manufacturing companies, the advent of a new iteration of industry starts to become an interesting topic of research. This next iteration of industry sets out to be more human-centric, *i.e.*, with a greater focus on the cooperation between man and machine, both in physical (*e.g.* robotics) and computational terms (*e.g.* artificial intelligence-based decision support tools) (Breque, De Nul, & Petridis, 2021). Furthermore, industrial resilience and environmental conscience are two additional main pillars of this industrial revolution, frequently harnessed by computational strategies that can minimize the unpredictability of the future via data-driven estimation and aid companies in opting for the most sustainable choices without great manufacturing impact.

This work tackles a three-echelon supply chain, which includes raw material suppliers, support warehouses, and main warehouse echelons. The focus of this work is on balancing stock on each echelon, since there are costs associated with keeping stock at each level, transporting stock and purchasing stock, but also serious shortage costs when raw materials do not arrive at lower level echelons for production on time. This work is a case study on the pharmaceutical industry, but can be applicable to enterprises with extensive manufacturing portfolios and which require inventory routing management. Nevertheless, the work is based on data from the pharmaceutical contract development and manufacturing organization *Hovione Farmaciência S.A.*

1.1. State of the art

Supply chain management is a widely researched topic, both in industry and academia. This research deals mostly with some specific topics of SC management, namely inventory routing optimization (layered warehouses), restocking policies optimization and (many-objective) optimization for decision support.

1.1.1. Restocking policies optimization

Generally speaking, replenishment (or restocking) policies can either follow an order cycle or restocking can take place when needed. The first is characterized by having a specific cycle time for each raw material bought from each supplier. According to Bhagwat and Sharma (2007), the total order cycle time can impact the supply chain response time and directly influence the satisfaction level of the

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customer. The latter restocking policy, often called order-up-to policy (OUT), is characterized by raw materials being purchased when needed (considering the lead-times required by each raw materials bought from each supplier). It is a riskier method and more prone to stock shortages. According to Sustrova (2016), "a universally suitable model for inventory management has not been developed, so in each specific situation, the optimal solution for the inventory model must be found as a derivative of existing models". Different companies in different industries require different restocking strategies.

Several publications found in academic literature directly tackle different strategies for restocking policies. The subject was first discussed and mathematically formulated by Harris (1913). The vast majority of the publications follow either order cycles or an order-up-to policy.

Regarding order cycle-based replenishment policies, most works suggest their replenishment intervals being adjusted through optimization (Adeinat, Pazhani, Mendoza, & Ventura, 2022; Baboli, Fondrevelle, Tavakkoli-Moghaddam, & Mehrabi, 2011; Huang, Yang, & Wang, 2021; Kumar & Mahapatra, 2021; Sebatjane & Adetunji, 2022; Zhou, Chen, & Ge, 2013) or artificial neural networks (Sustrova, 2016). Some of these works address perishable raw materials (Baboli et al., 2011; Huang et al., 2021; Sebatjane & Adetunji, 2022). Furthermore, Bakker, Riezebos, and Teunter (2012) review inventory systems with deterioration, often addressing the replenishment policies of this specific case of inventory management. Many published works are not directly focused on the issue of the replenishment strategies, but rather use standard order cycles for their specific purposes (El Saadany & Jaber, 2008; Hong & Hayya, 1992; Yu, Huang, & Liang, 2009).

As for OUT replenishment policies, most research done proposes dynamic policies (Babai, Jemai, & Dallery, 2011; Barron, 2019; Chen & Disney, 2007; de Oliveira Pacheco, Cannella, Lüders, & Barbosa-Povoa, 2017). Taleizadeh, Niaki, Aryanezhad, and Tafti (2010) consider independent time periods between replenishments in an inventory control system optimization; while not a typical order-up-to replenishment policy, its core principles end up aligned with the OUT ones. Clausen and Li (2022) use the empirical risk minimization principle to formulate a big data driven OUT inventory model, solved through machine learning algorithms.

An issue frequently associated with OUT replenishment policies is the bullwhip effect, where peaks and valleys of demand in production are echoed and intensified throughout the supply network, with suppliers often not able to fulfil the demand or doing so at a premium. This is an extremely undesirable phenomenon since it can either halt production due to lack of raw materials or increase their costs. According to Chen, Drezner, Ryan, and Simchi-Levi (2000), the bullwhip effect happens when demand variability increases along the supply chain. This also justifies the tendency for the bullwhip effect to take place with non-cyclical replenishment policies, since these have a much more unpredictable demand. Some research done in OUT replenishment policies also address this issue, *e.g.* Chen and Disney (2007), Constantino, Di Gravio, Shaban, and Tronci (2013), de Oliveira Pacheco et al. (2017) and Disney and Towill (2003).

While several methodologies can be followed for effective restocking, different industries often require different replenishment strategies. Companies with large product portfolios in very dynamic environments may require adjustable order cycles or even non-cyclical restocking policies to be resilient against changing conditions. Furthermore, more complex strategies for determining when to replenish a given raw material can be employed nowadays, with computational cost significantly reducing every year.

1.1.2. Inventory routing optimization

The problem of optimizing the amount of raw materials that are transported between support warehouses and the main warehouse, a specific case of inventory routing optimization, is also a widely researched topic. Theoretically, it is the combination of vehicle routing and inventory management (Coelho, Cordeau, & Laporte, 2014). While generally associated with suppliers and the transportation of the materials to their clients, any transportation of stock from a higher echelon to a lower falls in this category.

Coelho et al. (2014) provides a comprehensive review of publications on this topic. The authors classify each article according to time horizon, structure, routing, inventory policy, inventory decisions, fleet composition and fleet size (adapted from Andersson, Hoff, Christiansen, Hasle, and Løkketangen (2010)). According to the proposed classification, this problem can be classified as shown below.

- **Time Horizon:** Finite
- **Structure:** Many-to-one
- **Routing:** Direct
- **Inventory Policy:** Order-up-to-level
- **Inventory Decisions:** Stock-out
- **Fleet Composition:** Homogeneous
- **Fleet Size:** Unconstrained

Excluding the *structure* classification, since the many-to-one option was not a possibility suggested by the authors, no publication match the exact classification. Most works appear to deal with the transportation of finished products to retailers. For the problem at hand, the vehicle routing problem is not the crucial component, but rather the inventory management. The previously cited article by Zhou et al. (2013) addresses the issue, since the author's work is focused on a inventory control with a joint replenishment strategy.

1.1.3. Optimization for decision support

Results from a single-objective optimization algorithm are useful for decision-making, but the process is uncomplicated — only one optimal solution exists, therefore conclusions can be directly extracted from the results.

For multi-objective optimization with two objective functions, the process complicates and a decision-maker with field expertise is often required, to evaluate the results and decide which optimal scenario on the Pareto front best fits the company's necessities. While all optimal solutions to the problem, the objective functions values are often a compromise — choosing a solution with a small objective value in the first variable may have a larger value on the second, and vice-versa. Several publications address the usage of the Pareto fronts for decision support (Burger et al., 2014; Stummer, Kiesling, & Gutjahr, 2009; Wang, Lai, & Shi, 2011; Wierzbicki, Kruś, & Makowski, 1993). Bänsch et al. (2021) review decision support models in production environments, with a component of energy awareness.

Finally, for many-objective optimization with more than two objectives, while its usefulness on supporting decision is basically the same as for multi-objective optimization (with increased levels of information), it starts to suffer from a difficulty to convey which optimal solutions should be chosen. While for three objective functions it is still possible to show the results in a Pareto "surface", it is difficult to convey information in three-dimensional graphs on paper; furthermore, this representation becomes worthless for four or more objective functions. Two approaches to display how the objective functions values relate between each other are by parallel plots or by showing the pairwise Pareto fronts of objective functions (Fleming, Purshouse, & Lygoe, 2005; Fonseca & Fleming, 1998; Ibrahim, Rahnamayan, Martin, & Deb, 2016). These representation methods are only viable options for a maximum of around 10 objective functions, and for a limited population of optimal solutions. Nevertheless, both conditions are met in the scope of this work.

Coelho et al. (2014) state that a challenge in inventory routing problems is that they are typically very hard to solve. Regarding the study of replenishment policies, the main challenge has to do with the fact that no single type of policy can be used for every company, and often not even in the same company. Different materials may require different policies, either because of their urgency or their validity.

Complicated strategies may be able to account for these issues, but at the expense of complexity in the algorithms and modelling. Many-objective optimization also faces some challenges. While formulating multi and many-objective problems can simplify the models, as they often offer greater leeway for the optimization procedure, the algorithms that solve these problems tend to be more complex. Additionally, for many-objectives problems with a considerable amount of objectives, the decision making process becomes more complex.

A further challenge that these ever more data driven problems and models have is the requirement large amounts of accurate data. Additionally, optimization problems that consider many decision variables become increasingly lengthier, up to the point of not being able to generate solution in useful time, *e.g.* when an algorithm takes longer to obtain solutions than the period it is trying to optimize.

1.2. Proposed approach

This work provides a real-world application of a many-objective genetic algorithm to solve the combined problem of raw material replenishment and inventory routing, applied to a three-echelon supply chain of a pharmaceutical company. Due to the complex manufacturing portfolio of pharmaceutical enterprises, an OUT replenishment policy was chosen, with the formulation of the problem done in such a way that considers as optimization variables the batches to be ordered of each raw material, from each supplier, at each optimization day. This represents the interactions between the suppliers and support warehouses echelons on the proposed problem. Furthermore, the formulation integrates inventory routing optimization through an interaction between the support warehouses and main warehouse echelons. The quantities of each raw material to be transported on each day and from each support warehouse are the second set of optimization variables.

To optimize this problem a genetic algorithm (GA) was selected. While the genetic algorithm is one of the most common metaheuristic algorithms, its choice versus *e.g.* a particle swarm algorithm (PSO) was supported by the research by Alejo-Reyes, Mendoza, and Olivares-Benitez (2020), where the authors concluded for an inventory replenishment decision model the GA offered slightly better results with a considerable reduction in computational time. The authors also evaluate differential evolution algorithms, but while these offered a virtually nonexistent advantage in performance (0.02%), the computational time was smaller on the GA.

The optimization process chosen was a many-objective optimization. By considering several objective functions and arriving at multiple optimal solutions, this approach gives greater control to highly trained executives and decision makers, which can make their decisions based on the scenarios supplied by the algorithm and on their sensitivity to the relative weight that the different objectives have, which are often extremely complex and dependent on not easily quantifiable factors. Ultimately, the solution which minimizes the total cost may not be the most beneficial to a specific enterprise, given its characteristics and intricacies, hence the advantage of this type of algorithms.

The presented approach sets out to adhere to the key foundations of the industry 5.0, namely to be:

- **Human-centric** — decision-makers are paramount in evaluating the results of the many-objective optimization and using their field expertise decide on which solution best fits the company's goals.
- **Resilient** — based on actual historical and planned data, allows the optimization to be self-correcting and easily adapt to the future.
- **Sustainable** — costs with a direct impact on the environment (*e.g.* transportation costs) can be prioritized.

Additionally, the usage of the GA (an artificial intelligence-based algorithm) for the many-objective optimization is also set within the context of industry 5.0, since it leverages the power of these state-of-the-art algorithms.

The modelling done and the methodology followed differ from what was found in the literature. The most similar research was on Zhou et al. (2013); while the authors model similar costs, their research is focused multi-echelon supply chain, with n echelons upstream from the core enterprise and m echelons downstream, and the costs are analysed summed together, as a single-objective formulation. The majority of publications that address the joint problem of inventory routing and replenishment deal with the downstream supply chain, *i.e.* the replenishment of final product to retailers. An example of this type of research is the work by Wu, Zhou, Lin, Xie, and Jin (2021), which addresses the inventory routing of a two-echelon supply chain with time cycles and fuel consumption. In contrast, the approach proposed in this paper tackles the upstream supply chain, considering a time window and with a many-objective model, solved through a genetic algorithm.

2. Three-echelon supply chain

The problem in study intends on optimizing a three-echelon supply chain, organized in such a way as in shown in Fig. 1.

A simple description of how the supply chain operates is: at a production plant, several products can be manufactured, according to a given schedule; to produce a batch of each of those products, a certain quantity of raw materials is required. For manufacturing operations, the raw materials must be at the production plant's warehouse when the manufacturing starts. However, since keeping stock in such an in-demand warehouse is extremely expensive, a series of 3 support warehouses are used to refill the main warehouse when needed. These warehouses vary on size, location and stock keeping costs; as a general rule, the closer the support warehouse is to the main warehouse, the smaller and more expensive it is, but quicker and with smaller transportation costs to supply the main warehouse. Lastly, the support warehouses receive their stocks directly from the raw material suppliers. Each supplier can supply more than one product, and each product may be supplied by more than one supplier. Each combination of product and supplier has an associated cost and lead time; generally speaking, for a given product available by multiple suppliers, the lower the lead time, the higher the cost.

For simplicity, the units used are *Inventory Units, IU*, for both production orders and for storage keeping. Additionally, and since the data used for this optimization is sensitive corporate information, the data was anonymized, with the results bearing no physical meaning in the absolute sense, but maintaining the relative patterns between the objectives.

3. Formulation

The problem was formulated as a many-objective optimization, with 6 objective functions:

- $C_{Order} \equiv$ **Order cost**: corresponds to the direct costs of ordering and transporting raw materials from the suppliers.
- $C_{Hold} \equiv$ **Holding cost**: corresponds to the cost of keeping stock in the warehouse. Every warehouse has an holding cost, but the holding cost of the main warehouse is much higher than the support warehouses. This incentivizes stock to be kept on the support warehouses for as long as possible. This is a common practice, since these support warehouses can be bought on cheaper geographical regions, with a smaller rent, leading to smaller holding costs.
- $C_{Transport} \equiv$ **Transportation cost**: corresponds to the costs of transporting the materials from the support warehouses to the main warehouse. For simplicity, the transportation of raw materials from the suppliers to the support warehouses is neglected here and is included in the order costs.

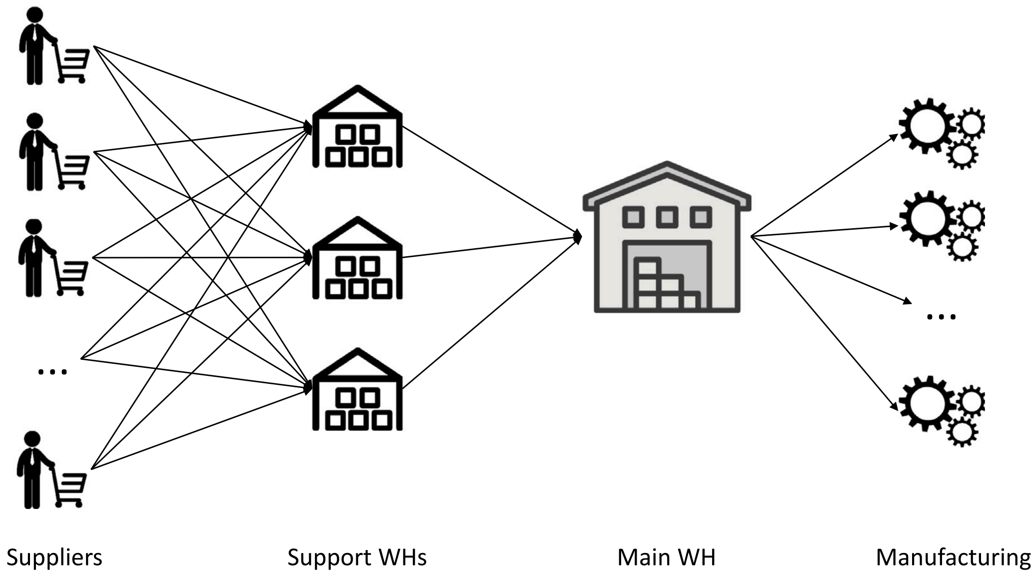

Fig. 1. Graphical representation of the three-echelon supply network in study.

- $C_{Shortage}$ ≡ **Main Warehouse Shortage cost**: corresponds to the costs of not having sufficient raw-materials for the production orders at the main warehouse. In such cases, the production orders may have to be postponed, leading to obvious and often hefty costs.
- $C_{Overflow}$ ≡ **Overflow cost:** corresponds to additional penalty costs when the warehouses' capacities have been surpassed. This is done to allow (but discourage) stock overflow, instead of constraining the optimization to disallow such behaviour.
- $C_{Shortage_{Int}}$ ≡ **Support Warehouses Shortage cost:** costs of not having sufficient raw-materials on the support warehouses to timely restock the main warehouse. It is separated from the shortage cost since while a shortage of raw materials at the main warehouse can lead to halting manufacturing processes, shortages of raw materials in the support warehouses may only affect the restocking of the main warehouse.

Each of the aforementioned individual costs can be mathematically formulated. Due to the complexity of the problem, the optimization will have a 15-day scope, with daily decisions, meaning that the algorithm evaluates for a 15-day period, optimizing decision variables with a daily precision. To do so, notation regarding each element has to be presented. This is shown in Table 1. Furthermore, the nomenclature used for the formulation of this problem consider five indices: i, j, k, g and t. Each of these indices refer to a dimension of the problem. Index i refers to the materials (if a variable has i as one of its indices, it means that it has values for all the m_i materials); index j refers to the suppliers (if a variable has j as one of its indices, it means that it has values for all the m_j suppliers); index k refers to the warehouses — when $k = 0$ the warehouse is always defined as the main warehouse, with the remaining m_k warehouses corresponding to the support warehouses; index g corresponds to the manufactured products, with m_g being the total number of products considered; finally, index t corresponds to the day, with values ranging from 0 to 15.

Considering the notation, each individual cost can be formulated. This formulation was mostly influenced by the work by Zhou et al. (2013), considering only the supply network side of the multi-echelon schematic proposed by the authors.

3.1. Costs formulation

$$C_{Order} = \sum_{t=0}^{15} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} \left[NT_{(i,j,t)} \cdot A_{(i,j)} \right] \tag{1}$$

Summarily, the order costs can be calculated as the total number of batches ordered throughout 15 days multiplied by their respective cost.

The costs of holding stock are generally not as straightforward as the order costs. Instead, the holding cost can be seen as an opportunity cost, since it is the indirect cost of unnecessarily occupying storage space. These costs are directly related to the inventory level of a warehouse at a given time and to the storage cost of each warehouse.

$$C_{Hold} = \sum_{k=0}^{m_k} \left[\left(\sum_{t=0}^{15} \sum_{i=1}^{m_i} max\left(0, S_{(i,k,t)}\right) \right) \cdot H_{(k)} \right] \tag{2}$$

Simply put, the holding costs correspond to the total stock of materials in each warehouse (per month) multiplied by each respective storage cost, which depends on which warehouse the products are being stored. The maximum function used simply tries to avoid negative values of $S_{(i,k,t)}$, which are possible for the main warehouse, when the required materials for production orders are smaller than the warehouse's stock. On such occasion, there are no inherent holding costs (since there is no stock to be held), and the consequences of the lack of materials will come from the shortage costs.

$$C_{Transport} = \sum_{t=0}^{15} \left[\sum_{k=1}^{m_k} DT_{(k,t)} \cdot f_{(k)} \right] \tag{3}$$

The expression shows that the transportation costs are simply the sum of fixed transportation costs of all trips made.

$$C_{Shortage} = \sum_{t=0}^{15} \left[\sum_{i=1}^{m_i} M_{(i,t)} \cdot \rho_{(i)} \right] \tag{4}$$

Since order cycles are not considered on this problem and raw materials are considered to be ordered only when necessary (minding the suppliers lead times), shortage costs are modelled as the unavailable quantity on each day and for every material multiplied by a shortage penalty and summed. If no raw material shortage takes place than this cost will be null. Note that this expression only evaluates unavailable quantities on the main warehouse; if a given material exists on a support warehouse but is lacking on the main warehouse then it is considered as unavailable stock. The shortage penalties of the materials will be heavily inflated to translate the importance of having the minimum amount of shortage costs possible.

$$C_{Overflow} = \sum_{k=0}^{m_k} \left[\left(\sum_{t=0}^{15} SO_{(k,t)} \right) \cdot O_{(k)} \right] \tag{5}$$

Table 1
Nomenclature used in the problem's formulation.

Order costs	
$A_{(i,j)}$	Individual material cost of raw material i ($i \in 1,\dots,m_i$) from supplier j ($j \in 1,\dots,m_j$), for one batch with quantity $B_{(i,j)}$
$B_{(i,j)}$	Standard batch size of material i from supplier j
$N_{(i,j,t,k)}$	Number of batches ordered of material i from supplier j at time t ($t \in 0,\dots,15$), to be delivered to support warehouse k ($k \in \{1,2,3\}$)
$T_{(i,j)}$	Average lead time of ordering material i from supplier j
Holding costs	
$H_{(k)}$	Storage cost per day per IU of warehouse k. This cost will be substantially higher for the main warehouse ($k = 0$).
Transportation costs	
$d_{(k)}$	Transportation distance between the support warehouse k ($k \in 1,\dots,m_k$) and the main warehouse ($k = 0$)
$DT_{(k,t)}$	Number of trucks required for the transportation of goods between the support warehouse k ($k \in 1,\dots,m_k$) and the main warehouse on day t
$f_{(k)}$	Transportation costs between the support warehouse k ($k \in 1,\dots,m_k$) and the main warehouse ($k = 0$). This includes all costs inherent to the transportation process
$Q_{(k,i,t)}$	Quantity of product i transported between warehouse k and the main warehouse, on day t
Shortage costs	
$M_{(i,t)}$	Quantity of unavailable raw material i on the main warehouse on day t
$\rho_{(i)}$	Shortage penalty per day and per IU of missing raw material i on the main warehouse
$sh_{(k)}$	Shortage penalty depreciating factor for each support warehouse k ($k \in 1,\dots,m_k$). Factor applied to the shortage penalty to decrease the shortage cost on support warehouses — the cheaper the warehouse, the less costly it is to have stock shortage.
Overflow costs	
$O_{(k)}$	Overflow costs per IU of material over the warehouse capacity of warehouse k
$SO_{(k,t)}$	Overflown total stock on warehouse k and on day t
Additional variables	
$RM_{(i,g)}$	Quantity required of raw material i for the production of a batch of product g
$I_{(i,k)}$	Initial stock of raw material i on warehouse k ($t = 0$)
$NT_{(i,j,t)}$	Total number of batches ordered of material i from supplier j at time t ($t \in 0,\dots,15$), agnostic to which support warehouse it is supposed to be delivered
$Pinit_{(i,k,t)}$	Amount of purchased raw material i that arrived at support warehouse k on day t for orders placed before $t = 0$
$PW_{(i,k,t)}$	Amount of purchased raw material i that arrived at warehouse k on day t
$P_{(i,t)}$	Amount of purchased raw material i that arrived at any support warehouse on day t
$PO_{(g,t)}$	Production schedule for product g ($g \in 1,\dots,m_g$) on day t. Each value can take either 1 or 0, with 1 corresponding to a production order of product g taking place on day t and 0 otherwise
$R_{(i,t)}$	Requirements of raw material i at day t
$S_{(i,k,t)}$	Stock of raw-material i at warehouse k and day t. Consider $k = 0$ for the main warehouse and $k \in \{1,2,3\}$ for the support warehouses
Tr	Truck capacity in IU
$W_{(k)}$	Maximum capacity of warehouse k measured in IU

The overflow costs are calculated simply by multiplying the stock above warehouse levels by an overflow factor. To avoid unfeasible and unrealistic scenarios, the overflown stock can only be up to 20% above each warehouses' capacity. This is enforced via a constraint, described ahead.

$$C_{Shortage_{int}} = \sum_{t=0}^{15}\left(\sum_{i=1}^{m_i}\left[\sum_{k=1}^{3} max\left(0, -S_{(i,k,t)}\right)\cdot sh_{(k)}\right]\cdot\rho^{(i)}\right) \tag{6}$$

The shortage cost of the support warehouses $C_{Shortage_{int}}$ presented in (6) is an extension on the shortage costs shown in (4). Instead of calculating a penalty cost for lack of raw materials for production (at the main warehouse), the shortage cost of the support warehouses calculates a penalty cost for lack of raw materials to transport to the main warehouse. The formulation only differs on the application of $sh_{(k)}$, a warehouse-specific depreciating factor, used to give less impact to the shortage costs of the support warehouses than to those of the main warehouse.

3.2. Additional expressions

A few additional expressions are used to obtain the variables used for the objective functions. The first is the calculation of the amount of purchased raw material that arrived at each support warehouse on each day, the variable $PW_{(i,k,t)}$. This is shown in (7). Additionally, (8) shows the amount of purchased raw material that arrived at any support warehouse, as the sum of the quantities that arrived on each support warehouse.

$$PW_{(i,k,t)} = Pinit_{(i,k,t)} + \sum_{j=1}^{m_j}\left(N_{(i,j,t-T^{(i,j)},k)}\cdot B_{(i,j)}\cdot\begin{cases}1, & t-T_{(i,j)}\geq 0\\ 0, & t-T_{(i,j)}<0\end{cases}\right) \tag{7}$$

$$P_{(i,t)} = \sum_{k=1}^{3} PW_{(i,k,t)} \tag{8}$$

The calculation of the total number of batches ordered of each raw material, from each supplier and at each day can be calculated as a simple aggregation of variable $N_{(i,j,t,k)}$. This is shown in (9)

$$NT_{(i,j,t)} = \sum_{k=1}^{3} N_{(i,j,t,k)} \tag{9}$$

The calculation of the daily raw material requirements should also be done, based on the production orders scheduled for the day. This can be done using the production orders schedule ($PO_{(g,t)}$) and the bill-of-materials of each raw material for each type of production order ($RM_{(i,g)}$). It is considered that each type of production is of fixed batch size, meaning that the raw material requirements will also be fixed. The calculation of the raw material requirements will then be calculated as shown in (10). This calculation only has to be done once, since both variables $PO_{(g,t)}$ and $RM_{(i,g)}$ have to be supplied, and are therefore immutable during the optimization.

$$R_{(i,t)} = \sum_{g=1}^{m_g} PO_{(g,t)}\cdot RM_{(i,g)} \tag{10}$$

Using these previous expressions, the stock of raw-materials ($S_{(i,k,t)}$) can be calculated. This expression is useful to translate a schedule of purchases of raw-materials, transportation of materials between warehouses and consumption of materials into a daily status of stock in each warehouse. The expression is shown in (11).

$$\begin{cases} S_{(i,k=0,t)} = S_{(i,k=0,t-1)} + \sum_{k=1}^{m_k} \left[Q_{(k,i,t)}\right] - R_{(i,t)}, & k = 0 \\ S_{(i,k,t)} = S_{(i,k,t-1)} - Q_{(k,i,t)} + PW_{(i,k,t)}, & k \neq 0 \end{cases} \tag{11}$$

The expression shown also implies that the initial stock levels of each warehouse at $t = 0$ have to be supplied ($I_{(i,k)}$).

The calculation of the quantity of unavailable material on the main warehouse for the daily production requirements ($M_{(i,t)}$) is shown in (12)

$$M_{(i,t)} = max\left(0, -S_{(i,k,t)}\right), \quad k = 0 \tag{12}$$

This expression takes into account the formulation of $S_{(i,k,t)}$ as shown in (11), observing the stock for the main warehouse ($k = 0$). If the stock of a given material on a given day is smaller than 0, it means that the required material for the day was higher than the available. Such values are stored in variable $M_{(i,t)}$; when the requirements are fulfilled $M_{(i,t)}$ is null.

The following expression deals with the calculation of the required number of trucks for a given day t, between the support warehouse k and the main warehouse, shown in (13).

$$DT_{(k,t)} = ceiling\left(\frac{\sum_{i=1}^{m_i} Q_{(k,i,t)}}{Tr}\right) = \left\lceil \frac{\sum_{i=1}^{m_i} Q_{(k,i,t)}}{Tr} \right\rceil \tag{13}$$

The ceiling operator is used in the calculation of the required number of trucks since the value must be an integer, and if the capacity of the truck is exceed in a single IU, then a new truck has to be used.

Finally, the calculation of the overflown stock per warehouse k and day t is shown in (14).

$$SO_{(k,t)} = max\left(0, \sum_{i=1}^{m_i} max(0, S_{(i,k,t)}) - W_{(k)}\right) \quad k \in \{0,1,2,3\} \tag{14}$$

On the above expression, the inner *maximum* function is used to discard negative stock values, which derive from unfulfilled production stock requirements (only when $k = 0$) and should not decrease the total warehouse stock. On the other hand, the outer *maximum* function simply discards negative $SO_{(k,t)}$ values, which regard warehouse stocks that have not overflown.

Two constraints are applied to the formulation in study. The first simply requires all variables to be non-negative. The second constraint is shown in (15).

$$\sum_{i=1}^{m_i} S_{(i,k,t)} \leq W_{(k)} \cdot 1.2, \; k \in \{0,1,2,3\}, \; t \in \{0,\dots,15\} \tag{15}$$

The constraint formulated simply establishes that the total stock at each warehouse and for each day must not be larger than 20% above the warehouse's capacity. This is employed to constrain the optimization from unrealistically filling the warehouses above their limit. As previously mentioned, this limit can be surpassed at the expense of the overflow cost.

The complete formulation of the problem is shown in (16).

$$\begin{aligned} \min_{\Omega} \quad & F_1 = C_{Order} \\ & F_2 = C_{Hold} \\ & F_3 = C_{Transport} \\ & F_4 = C_{Shortage} \\ & F_5 = C_{Overflow} \\ & F_6 = C_{Shortage_{Int}} \\ s.t. \quad & \Omega \geq 0 \\ & \sum_{i=1}^{m_i} S_{(i,k,t)} \leq W_{(k)} \cdot 1.2, \\ & \qquad k \in \{0,1,2,3\}, \; t \in \{0,\dots,15\} \end{aligned} \tag{16}$$

Table 2
Hyperparameters and dataset settings.

Parameter	Value
m_i	15
m_j	17
# product types	30
t_{max}	15
Max generations	200
Crossover fraction	0.75
Population size	250
Function tolerance	10^{-12}
Constraint tolerance	$2 \cdot 10^6$

It is important to mention that the formulation does not resort intensively to constraints. This happens in part due to the fact that the optimization is a many-objective optimization, allowing for greater freedom within the optimization. An example of this is the use of shortage costs. Instead of calculating shortage costs, the optimization could simply enforce that the stock would always have to be in sufficient amounts for production. Alternatively, by using the shortage costs, the optimization can be run and the resulting shortage costs have to be then considered.

The set of decision variables Ω and the variables that must be supplied Φ can be seen in (17) and (18).

$$\Omega = \{N_{(i,j,t,k)}, Q_{(k,i,t)}\} \tag{17}$$

$$\begin{aligned} \Phi \quad = \quad & \{A_{(i,j)}, B_{(i,j)}, T_{(i,j)}, H_{(k)}, d_{(k)}, f_{(k)}, \\ & W_{(k)}, Tr, \rho_{(i)}, Pinit_{(i,k,t)}, I_{(i,k)}, PO_{(g,t)}, \\ & RM_{(i,g)}, O_{(k)}\} \end{aligned} \tag{18}$$

4. Results analysis

Table 2 shows the hyperparameters for the optimization ran, as well as the dataset settings, namely, the number of raw materials or suppliers considered. The total number of decision variables is 12 960. Additionally, the production schedule considered (encompassed in variable $PO_{(g,t)}$) included a total of 55 production orders, for the baseline optimization ran. The algorithm used for the optimization was the Matlab's *gamultiobj*, a variant of NSGA-II. An initial optimization was ran, and the results are shown in the parallel plot of Fig. 2. Each connected line corresponds to the objective function values of the corresponding solution. The colour coding used simply compares the total cost of the solution, and it is mostly useful to distinguish between scenarios. Furthermore, Fig. 3 shows every pair of Pareto fronts between the objectives.

The grey line from Fig. 2 corresponds to the result from a single-objective optimization, optimizing the total cost as the sum of the 6 other costs ($C_{Total} = C_{Order} + C_{Hold} + C_{Transport} + C_{Shortage} + C_{Overflow} + C_{Shortage_{Int}}$), with weights considered all at value 1. The results show that while the total cost is indeed lower than the lowest scenario from the many-objective optimization (837 414.0 vs. 874 582.9), it may not always be the optimal solution, and it is safer for a decision-maker to decide based its professional judgment. While the holding and overflow costs are lower than the results from the many-objective optimization, the order cost is only average and the support shortage cost is much higher. It is important to mention that possibly the many-objective optimization would evolve into having solutions similar to the single objective one, given enough computational time. Since the many-objective optimization is a more computationally complex process than the single-objective optimization, it makes sense that it would require additional time to achieve comparable results.

Regarding the results from the many-objective optimization, a few conclusions can be taken from the figures shown:

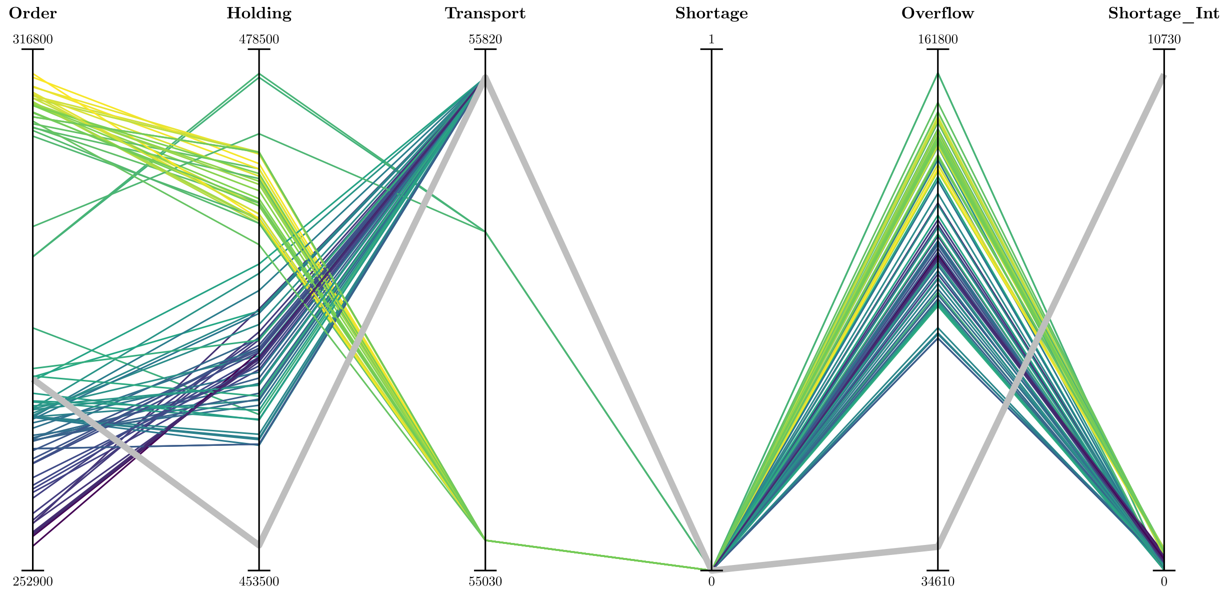

Fig. 2. Parallel plot of the different objectives for the different optimal solutions of the baseline scenario. Each line corresponds to a single optimal solution.

- Order and holding costs are approximately proportional. This makes sense: purchasing more raw materials will require additional costs of holding said stock.
- Larger order costs lead to slightly smaller transportation costs. This simply means that if stock is not bought in such large quantities, it is instead transported from the support warehouses. This can have additional consequences, namely
  - Overflow costs increase, as expected. Since stock bought on lower order costs solutions is sufficient for the production orders (seeing as the shortage costs are always null), purchasing larger quantities of it will lead to higher overflow costs.
  - Support shortage costs appear to be less predictable, since while most high order cost scenarios have a higher value, there are instances of high order cost with lower support shortage cost, and with lower order cost and higher support shortage cost. This derives from **when** the increased support shortage costs take place. For example, a scenario may order large amounts of raw materials on the second week of the optimization, but during the first there may not be sufficient amounts of it in the support warehouses, leading to an increase in support shortage costs.
- Transportation costs tend to concentrate at certain values, due to the fact that these costs are proportional to the number of trucks that move between the warehouses. This means that there is a finite and discrete number of possible transportation costs, hence the banding that appears to take place.
- A very well defined proportionality can be seen between holding and overflow costs — all solutions have non-null overflow costs, and the holding costs are applicable to the overflown stock as well.
- Optimal solutions with high total costs (represented by the yellow and light green points) appear to have high values on almost all types of costs. The exception to this is the transportation costs, having the smallest cost of all solutions. This means that while obviously not the best solution to the problem, if a decision-maker really prioritizes small transportation costs (and all it entails), then those solutions may be the best choices.

Shortage costs are always null in all optimal scenarios — this means that for this scenario there is no possible outcome that extracts any advantage in increasing the shortage costs in favour of any other cost. This may also derive from the fact that the shortage costs are extremely inflated, compared with other costs, since they are some of the most catastrophic types of costs, as they may lead to halting manufacturing processes. While this cost may be redundant, keeping it as an objective function shows that the optimization performs as expected.

Even though the optimal scenarios appear to vary considerably, it is important to note that the total cost of the optimal scenarios does not vary much, with the maximum total cost being only 12.7% larger than the minimum. The figures show that there are multiple scenario worthy of consideration, given their overall performance. By using such results, decision-makers could make data-driven decisions, knowing the expected costs of each solution and combining their expertise to arrive at an adequate choice according to their industry and company goals.

4.1. Additional scenarios

To further validate the models, two additional scenario were optimized. These scenarios kept the exact same parameters and dataset as the one shown on the previous section and on Table 2, with only a difference: the total number of production orders per month increased from 55 in the baseline scenario, to 107 in the first variation and to 171 in the second. This intends on testing a scenario where the same company and for the same period is faced with a different production schedule with varying degrees of complexity. The parallel plots for these two scenarios are shown in Figs. 4 and 5.

The results show some similarities and differences with the baseline scenario. The clearest similarity is the overall distribution of the solution. On both variations, the highest total-cost solutions (shown as the yellow/light green lines) have high order costs, low transportation costs and higher overflow costs. Both variations are able to obtain solutions with null or almost null overflow cost.

A very important difference found in both variations is the fact that the single objective solution is not the best out of all the summed many-objective solutions. This means that the single-objective optimization does not bring any advantage. While it is not possible to know definitely the reasons for this, it can be assumed that the larger flexibility provided by the many-objective optimization allows for better and more variate results.

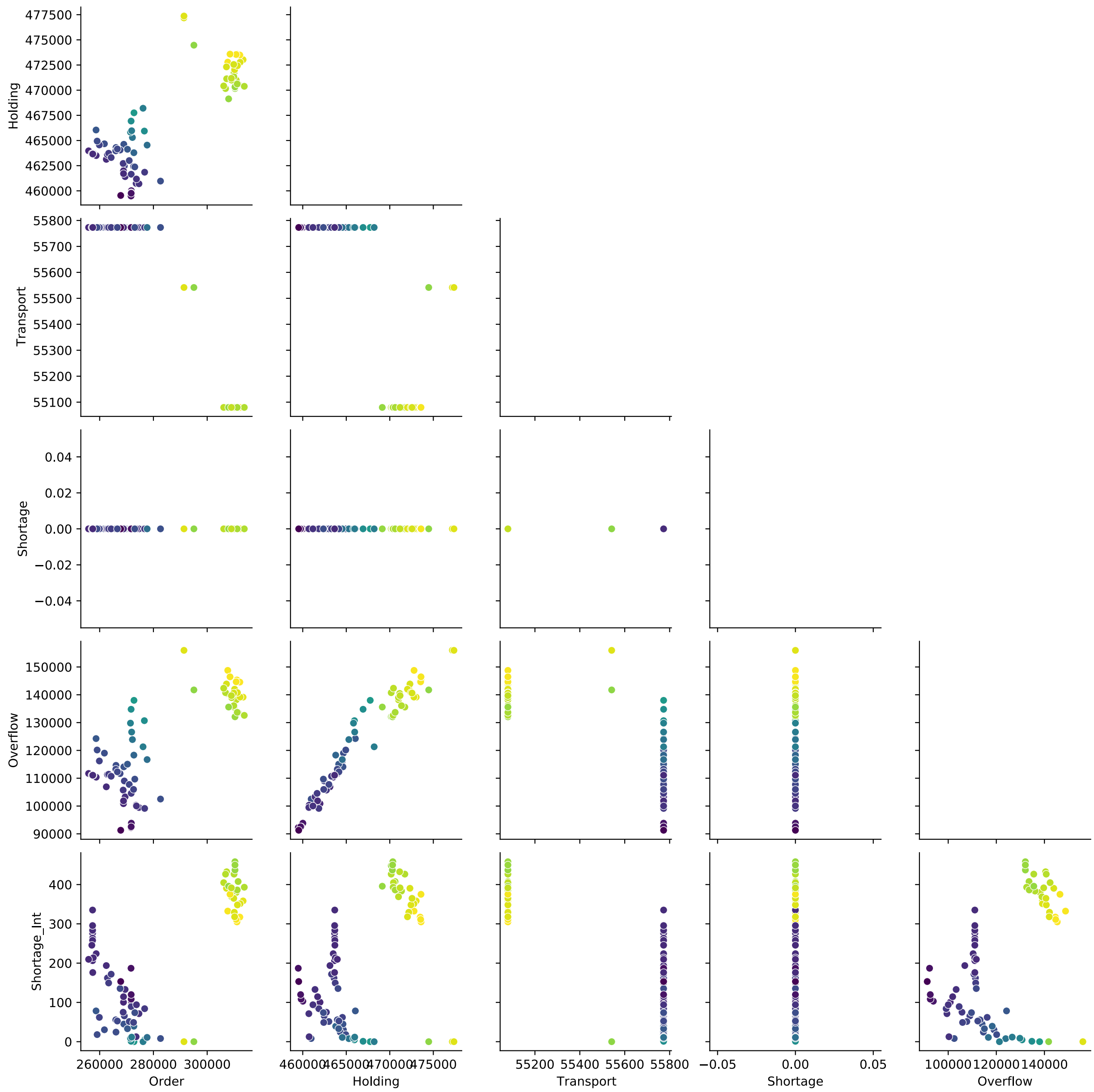

Fig. 3. Matrix representation of the Pareto fronts between the objectives of the optimization.

5. Conclusions

On dynamic industries, such as the pharmaceutical one, and on enterprises with large product portfolios and consequent complex raw material requirements, establishing a replenishment policy based on planned manufacturing operations is crucial. Furthermore, obtaining the quantities of raw materials to order from each supplier in tandem with the quantities to transport between warehouses (as a typical inventory routing problem) from a combined optimization process proved to be a powerful method. While this method was tested for the pharmaceutical industry, it could be applied to many other manufacturing industries, and especially useful for industries with dynamic raw material requirements and internally organized within warehouse levels.

This paper showed how companies can use and extract real value from the results of multi/many-objective optimization. Two major benefits of the many-objective optimization can be highlighted. The first has to do with the active necessity of a human decision-maker. While this may seem like a disadvantage, it is actually extremely important since it increases accountability, simplifies the modelling of the problem, actively exploits the expertise of highly-trained professionals, and generates multiple optimal solutions that prioritize different objectives of the problem. This is very much in accordance with one of the pillars of the Industry 5.0: human-centric. The second benefit of using many-objective optimization is its capacity to frequently provide better results than the single objective optimization, even when comparing the results converted to a single-objective analogue. This behaviour was also verified in the scientific literature, see *e.g.* Mahrach, Miranda, León, and Segredo (2020). Some possible explanations for this phenomena may have to do with the algorithm's tendency to better avoid local minima, as more scenarios are tested, to provide solutions that have better performance with different objectives. In Mahrach et al. (2020) it is also indicated that the multi-objective optimization algorithms perform better that single-objective ones (especially in large problems or when the objectives are strongly correlated) due to its "intrinsic capacity to maintain diversity within a population".

The adoption of a joint inventory routing/replenishment policy as a many-objective optimization was shown to provide useful results.

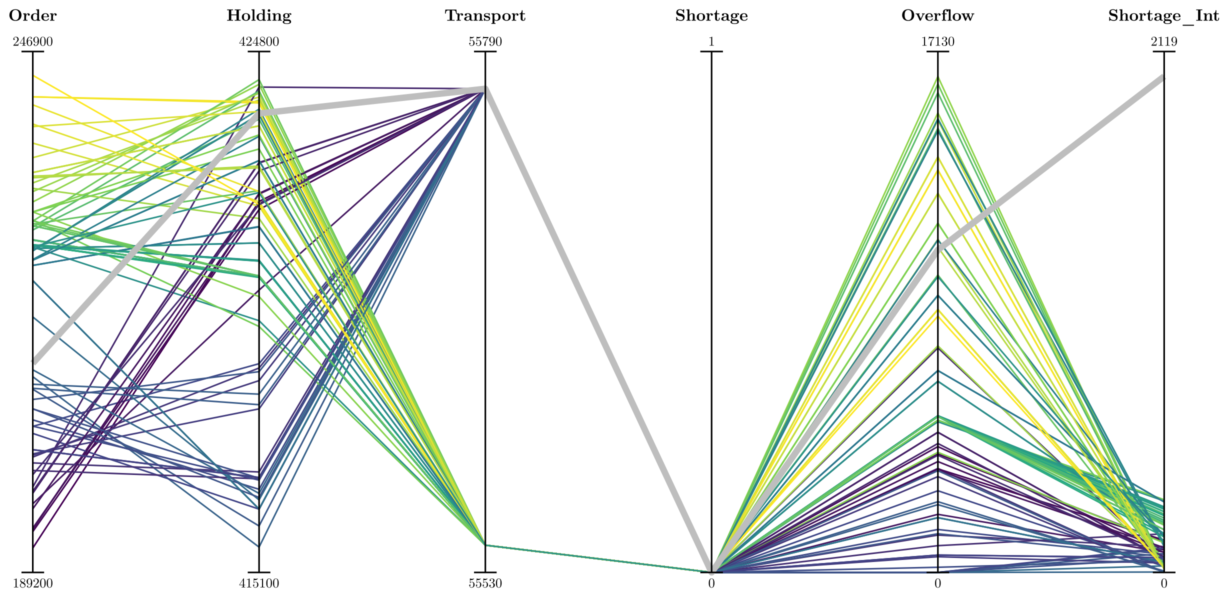

Fig. 4. Parallel plot of the solutions obtained for the first variation of the problem (107 production orders). Grey line corresponds to a single-objective solution.

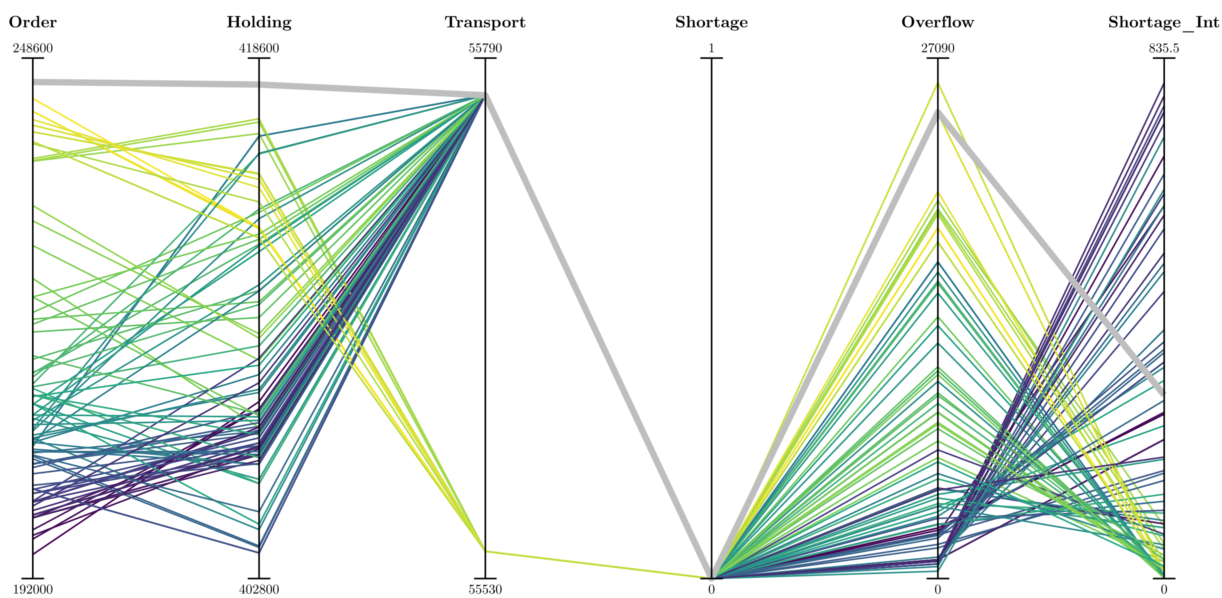

Fig. 5. Parallel plot of the solutions obtained for the second variation of the problem (171 production orders). Grey line corresponds to a single-objective solution.

These results are especially practical for pharmaceutical management, to make more data-driven decisions, more eclectic than other methodologies, as the replenishment policies take into account the inventory routing between support and main warehouse and vice-versa — all while providing multiple scenarios for the decision-makers to choose from, therefore increasing visibility and accountability.

The key issues found have to do mostly with how well the reality is modelled. While the models are fairly simple, the parameters used on them are usually difficult to accurately estimate (*e.g.* how much does each inventory unit cost in a warehouse), leading to errors in the calculated values. The effects of this are generally mitigated with many-objective but paramount in single-objective optimization. The reason for these effects are that in many-objective optimization the parameters have only to be correct in relation to each other, *e.g.* the relation between the holding cost (per inventory unit) at the main warehouse and at one of the support warehouses should be correct, but the actual holding costs are not important. In contrast, in single-objective optimization, the over or underestimation of a parameter may deeply affect the final results in an unintentional way.

Another issue found is the computational demand that the optimizations ran took. An optimization such as the ones shown (with more than 12 000 decision variables) can take almost 24 h to run. This value seems to be reasonable for an optimization that deals with a 15-day horizon, but it is important to note that only 15 raw materials and 17 suppliers were considered and that the optimization was only ran for 200 generations. This issue is, however, expected to be less present in the future, as the computational capacity improves and the algorithms are often simplified.

One final issue that may be the most important of all is the fact that the decision-making process can start to become overwhelming for decision-makers, when a large number of objectives – and consequently solutions – is reached. Making decisions based on six objectives may be difficult. Further research on this topic may be explored, namely on the development of decision support tools for many-objective optimization results.

CRediT authorship contribution statement

João A.M. Santos: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing review & editing, Visualization. **João M.C. Sousa:** Conceptualization, Methodology, Validation, Writing review & editing, Supervision, Project administration, Funding acquisition. **Susana M. Vieira:** Conceptualization, Methodology, Validation, Investigation, Writing review & editing, Supervision, Funding acquisition. **André F. Ferreira:** Validation, Resources, Data curation, Writing review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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