Innovative approaches to optimal blood supply chain management problems

Sara de Jesus Franco

Instituto Superior Técnico, Lisboa, Portugal

October, 2022

Abstract

Blood is vital to life, playing a necessary role in various basic human needs. However, it is perishable, unique and both its supply and demand are uncertain as its availability depends on voluntary and unpaid donations and future events are unpredictable. The essential nature of blood, perishability, uniqueness and uncertainty increase the complexity of managing its supply chain. In fact, the Portuguese case presents inefficiencies, particularly high wastage levels for platelets. Thus, it is of great importance to have an efficient and sustainable method, able to fix existing inefficiencies. Hence, a literature review was carried on the blood supply chain and other perishable supply chains, namely the agro-food supply chain, to find possible knowledge transfers from the agro-food to the blood supply chain. Therefrom, an innovative model was developed, mainly focused on minimizing waste and increasing the quality of transfusions, which introduces a maximum age, specific for each demand node, corresponding to the maximum age for transfusions and beyond which demand nodes return blood to the blood center, to be redistributed to other demand nodes. The model was applied to the Portuguese case, for pools of platelets with pathogenic reduction, and the results showed that, although in relatively modest quantities, redistributing blood is beneficial for reducing its waste. Additionally, the average age of transfusions and the level of substitutions presented better results. Additional analysis proved that further wastage reduction could be achieved when considering products with higher shelf lifes.

Keywords: Blood, Blood Supply Chain, Agro-food Supply Chain, Perishable Products, Optimization, Wastage.

1. Introduction

Blood is essential to life, playing a necessary role in basic human needs such as breathing, nutrition, regulation and protection of the human body. However, it is a perishable good, with limited Shelf Life (SL) after which it must be discharged. Also, blood products (Whole Blood (WB), Red Blood Cells (RBCs), Platelets (PLTs), Plasma and Cryo (Cryoprecipitate Antihemophilic Factor)) require high service levels, such as specific storage and transport conditions, and each blood product has different key utilities. Besides, blood is a unique product, as it cannot be replaced and has no substitutes. Its availability mostly depends on voluntary and unpaid donations, so the blood supply is uncertain over time, along with demand, which is also uncertain. Since blood is vital, it should always be available when needed, but its wastage should always be avoided. The importance of the BSC is self-evident, but its complexity is perhaps less obvious, being the management of blood a concerning problem. Although there are existent technological developments in blood substitutes, the need for blood donations will always exist [1,2].

The Blood Supply Chain (BSC) is constituted by blood facilities, which include Collection Sites (CSs), Blood Centers (BCs) and Demand Nodes (DNs), that ensure its functioning and the safety and quality of the blood, throughout its four main stages: collection, production, storage and distribution [3]. In order for blood facilities to meet blood supply and demand, they need to be strategically and efficiently designed and incorporated in the BSC, without compromising health care.

Thus, the aim of this dissertation is to present and characterize the BSC and provide an overview of the most relevant approaches to deal with its most relevant problems. The end goal is to find the extent to which innovative approaches, based on other perishable products, can be applied to the management of the BSC and how such approaches can be tailored to fit its specific characteristics. From this, a mathematical optimization model will be developed, using the most relevant innovative approach, based on the findings of the overview on other perishable products SC management problems, and applied to the BSC, particularly for the Portuguese case and inefficiencies.

2. The Portuguese blood supply chain

Instituto Português do Sangue e da Transplantação, IP (IPST) is the entity responsible for the regulation and management of all blood-related activities in Portugal. It is structured into 3 territorially decentralized services, the *Centros de Sangue e da Transplantação* (CSTs), that ensure the availability of blood to the entire country: CST of Lisbon (CSTL) covers the Southern Region (Lisboa e Vale do Tejo (LVT), Alentejo and Algarve regions), CST of Coimbra (CSTC) covers the Central region, and CST of Porto (CSTP) covers the Northern Region [4]. The Portuguese BSC englobes four main processes – collection, production, inventory and distribution –, to be further described in this work. The CSTs are responsible for the processes of collection, processing, storage and distribution of the blood products and its flow articulation with DNs in each respective region, and some hospital blood units run by IPST are also qualified to perform collection [5].

Moreover, data from IPST on collection and transfusion is analyzed and the most relevant trends are identified. Regarding the collection, data shows that both the number of donations and donors have been decreasing over the last years, with consistently negative annual variation rates, specially in 2020 due to COVID-19. From all the blood donations performed in 2020, most were collected by IPST, highlighting the importance of IPST and its activities developed for the collection of blood. Concerning transfusions for RBCs, comparing the transfused with the collected units, it is concluded that the LVT region is not self-sufficient, requiring more than the collected units and, consequently, the contribution of other regions of the country. As for PLTs, these are the most wasted products - over 50% of PLTs from WB and about 34% pools of PLTs with PR are wasted.

Therefore, BSC management is very important, particularly in the Southern region of Portugal, where there's more collection while, at the same time, insufficient local supply and high levels of waste.

3. The blood supply chain

To further support the knowledge of the discussed and reported for the Portuguese case, and to identify what has already been made to addressing the existing problems of the BSC, a literature review on the BSC and BSC management is performed.

3.1. Features of the blood product

The ABO blood system classifies blood according to the presence of agglutinogens/antigens on the surface of the RBCs, and agglutinins/antibodies in the Plasma. Incompatibility occurs when someone with a certain agglutinin receives blood with the same agglutinogen. Blood of type A has A antigens and anti-B antibodies, and blood of type B vice-versa, while blood of type AB has both A and B antigens no antibodies in the Plasma, and blood of type O has no antigens and both anti-A and anti-B antibodies [6]. The Rh system

classifies the blood according to the presence or absence of the Rh factor/antigen on the cell membranes of the RBCs. If present, the blood type is complemented with a positive sign, and if absent, with a negative sign. In order to avoid adverse reactions from transfusions, it's important to know the blood types of the donor and the recipient before transfusion. If there is shortage of the same blood type, blood type substitutions may occur according the blood type compatibilities and preference orders, as follows in table 1.

Table 1: ABO/Rh system blood types' distribution, compatibilities and preference order for substitutions (from "1", the most preferable substitution, to "8", the least preferable substitution) (adapted from Najafi et al. (2017)) [8].

Donor	Recipient							
	O-	O+	A-	A+	B-	B+	AB-	AB+
O-	✓1	✓2	✓3	✓4	✓2	✓4	✓4	✓8
O+	×	✓1	×	✓3	×	✓3	×	✓7
A-	×	×	✓1	✓2	×	×	✓3	✓6
A+	×	×	×	✓1	×	×	×	✓5
B-	×	×	×	×	✓1	✓2	✓2	✓4
B+	×	×	×	×	×	✓1	×	✓3
AB-	×	×	×	×	×	×	✓1	✓2
AB+	×	×	×	×	×	×	×	✓1

The blood's 4 main components are Plasma (that transports blood cells with nutrients, wastes, antibodies, proteins, etc.), RBCs (that contain hemoglobin responsible for carrying oxygen from the lungs to the cells and returning carbon dioxide to the lungs), white blood cells (that protect the body against infections) and PLTs (that help the coagulation process at the site of injury) [7]. When blood is donated, two collection methods can be used: WB or apheresis, in which the blood components are obtained separately, each having its own characteristics, SL and storage conditions.

3.2. Literature reviews on the blood supply chain

Given its importance, the BSC has motivated researchers, which in the 20th century started to analyze the whole SC, describing advances and opportunities for further research. There are 4 main reviews on the BSC, starting with Beliën & Forcé (2012), which reviews on the inventory and SC management of blood products by covering 98 existing works published up to 2010 [1]. Then, Osorio et al. (2015) performs a structured review of the literature on quantitative models on the BSC, including papers published up to 2014, aiming at the design of a framework for decision making, providing contributions and finding gaps. From this, the authors divide the BSC into four main stages - collection, production, inventory and distribution -, and conclude that there is a clear need for modelling the entire process flow in the BSC [2]. More recently, Pirabán et al. (2019) explore BSC studies from 2005 to 2019, highlighting research gaps and interesting directions for future works [9]. Lastly, Meneses et al. (2022) review the most relevant optimization literature and existent mathematical models on the BSC, and develop a conceptual model of each BSC identified problem, composed by the main decisions involved, inputs and parameters on the strategic and tactical planning levels, and identify a research agenda of the literature gap for further investigation. The main literature gap identified by the authors is the limited consideration of the full integration of BSC decisions from the 3 planning levels [10].

3.3. The blood supply chain stages

3.3.1. Collection

Collection is responsible for obtaining, from donations, the quantity of blood and blood products needed to satisfy the demand and feed the rest of the network. Donations can be from schedules or walk-in donors at the collection locations, which in Portugal can be CSTs, hospital blood units, mobile venues or bloodmobiles.

There are two possible methodologies for collection: WB or apheresis. WB collection is the most common method, and consists of extracting approximately 450 ml of blood with the same composition as that circulating in the donor, into a single mother bag, to later be separated into its components by fractionation at the production stage. Apheresis is a method that extracts one or more specific isolated blood components into separated bags, and returns the remaining blood to the donor [2,9]. The yield of blood products by apheresis is greater than that of WB collection, withdrawing, per year, a greater amount of blood from one donor. However, it carries higher costs since it requires more expensive equipment, and it is more time consuming demanding a greater time commitment from the donor [9].

There are two types of CSs: fixed or temporary CSs. Fixed CSs include BCs (the CSTs, in Portugal) and hospital blood units, which are permanently equipped with the necessary material for donations and can perform both WB and apheresis donations. Temporary CSs include mobile venues, which only perform the WB method and are not permanently equipped, so the necessary material needs to be transported to the respective location, and bloodmobiles, which can perform only WB collection if single mobiles or both WB and apheresis if double mobiles. The greatest difference between fixed and temporary CSs is the location, as the temporary sites can move between geographic regions. However, fixed sites offer a greater capacity for blood products and staff, and more equipment, which implies higher establishment costs. For the Portuguese case, the collection sessions in mobile venues are organized by the CSTs together with donor associations, local authority bodies or even companies and cultural associations. Also, the blood collection process is standardized and complies the following processes: donor registration, triage, collection and post-donation vigilance.

3.3.2 Production

Production is the stage where blood is received after collection at the BCs to be tested and then possibly fractionated into RBCs, PLTs, Plasma and/or Cryo [2]. In Portugal, the production facilities are located in the CSTs and in some hospital blood units' laboratories.

Testing the donated blood is a rigorous process to ensure the quality, compatibility and safety of blood. For that, firstly the ABO/Rh blood type is determined, and then tests are performed to inquire about the existence of diseases and transfusion-transmittable infections, such as HIV or hepatitis B and C, for the Portuguese case. In addition, more different sets of screening tests can be selected, considering the infection prevalence rates of the donors [9,11]. The processing of blood into its components (fractionation) is performed using a centrifuge machine to separate blood components according to their density, depending on the velocities and processing times of centrifugation [12]. In Portugal, the components processed in larger quantities are RBCs, then PLTs and Plasma and, in much lower quantities, Cryo [5]. Also, for all these blood products the removal of the white blood cells, or leukocytes, is mandatory [13]. For the specific case of PLTs (precisely, pool of PLTs), these are actually obtained after processing buffy coats, which are simply a concentration of all the White Blood Cells and PLTs isolated from Plasma and RBCs by centrifugation. More precisely, it takes four units of buffy coats to obtain a pool of PLTs. The pools of PLTs need to be assembled, at maximum, 24 hours after the collection of the buffy coats, and then can be used according to their SL or be inactivated by Pathogenic Reduction (PR), which reduces transfusion-transmitted infections, protecting from infectious agents and potentially impact the safety of blood transfusions [14], as well as it increases the PLTs short SL from 5 to 7 days [5,15].

3.3.3. Inventory

Inventory is the stage that has received the most attention in the literature. The storage of blood can take place at BCs or hospital blood banks, and it can be simply defined as the process of properly preserving blood products suitable for transfusion, according to the specific storage conditions of each product to safeguard its quality.

Inventory control policies are what defines the product's storage procedures for all the storage locations from the network. These can be continuous or periodical, which are the most widely used,

according to [16]. The most common types of periodical policies are the Fixed Reorder Quantity policy (*R*,*Q*), the Order-Up-To-Level policy (*R*,*S*) and the Minimum/Maximum inventory policy (*R*,*s*,*S*), where *R* is the periodicity of review, which specifies the amount of time between analysis of inventory levels, *Q* is the fixed order quantity, *S* is the target level and *s* is the reorder point (or the safety stock). Blood issuance policies are also set in this stage, the most mentioned in literature are: FIFO (First-In-First-Out) and LIFO (Last-In-First-Out), the most common, and FEFO (First-Expired-First-Out). The first corresponds to using firstly the products that have been stored for the longest, the second to using firstly the products that have been stored most recently, and the third to firstly using the products with the shortest expiry date [9].

Inventory can be of two types, assigned and unassigned. When blood arrives to the DNs, it is tagged as unassigned inventory, meaning that it is not yet reserved for any patient. Then, when blood is required, units enter the pre-transfusion crossmatching testing process, to test the compatibility between patients and blood products. If approved, the crossmatched units assigned to patients are put aside and classified from unassigned to assigned inventory. The unused or incompatible crossmatched units of blood then return to the unassigned inventory [9]. Blood units also return to the unassigned inventory after the crossmatch release period (maximum time a blood product unit is stored in assigned inventory before it is returned to unassigned inventory), which should be as short as possible [2]. The ratio between the total number of crossmatched units and transfused units is called the crossmatch-to-transfusion ratio (C/T ratio), which should be as close as possible to 1, preventing wastage [17].

In Portugal, although there's not much information available from IPST on inventory management, it can be assumed that the FIFO issuing policy is the adopted one, once that it is considered to be the most efficient issuing policy to prevent wastage, minimize shortages and outdated units, and average inventories. It is also assumed that the review periodicity is of 1-day for the DNs to place orders to the CSTs, as it is the most common review policy [8,17].

3.3.4. Distribution

Distribution happens whenever there is movement of blood between facilities in the BSC. It involves two main logistics – shipment and distribution to DNs. Shipment runs right after the collection of blood and blood products, using vehicle fleets or shuttles, and distribution to the DNs from the BCs runs through vehicle fleets, that must ensure the timely delivery of blood products [18]. Vehicle fleets normally transport blood from the CSs to the BCs, while bloodmobiles return to the BCs with the blood collected, at the end of the day, and deliver blood from the BCs to the DNs. The vehicles can also pick up unused blood products from the DNs and collect fresh blood from the mobile venues and the bloodmobiles then returning to the BC. Shuttles are used to assist the mobile venues and bloodmobiles, supplying them with any necessary resources. In case of shortages in a certain location, and over-supply in another, blood products in inventory may also be transported between similar facilities, within a process called Lateral Transshipment.

For the Portuguese case, official information on this stage is also scarce in IPST, but it is known that daily transportation of blood and blood components with controlled temperature takes place between the three CSTs headquarters, with the transport assured by external contracting. Also, there is no IPST fleet for the transport of Plasma at -25ºC and the cost of acquiring a vehicle with this specific temperature controlled conditions is very high [19].

3.4. Main gaps and methodologies from literature

For the collection stage, literature is mainly focused on donor behavior and the location and configuration of the CSs, and there is limited literature on collection policies and the allocation of donors to the two collection methods, or the relationship between the efficiency and costs of the two. The production stage is the least studied stage, with the existing literature giving little attention to the proportion of products obtained from WB or apheresis, whereas inventory holds the majority of the literature. Lastly, the distribution stage problems, such as product allocation to the production centers and collaborative schemes, are not very addressed and need more attention. In addition, there is few literature dealing with the entire model and the connections and interrelations between the multi-echelons and the three main planning levels [10]. This is a very important gap identified, as modelling the entire process flow in the BSC can help to identify bottlenecks, evaluate policies from a whole-system perspective, minimize the impact of uncertainty in supply and demand, and even recognize constraints in the preceding and succeeding echelons, avoiding the bullwhip effect [2,9].

Regarding the main methodologies used in literature, most approach the uncertainty of the BSC parameters. Hence, mathematical optimization techniques are frequently applied to address BSC problems, defining the parameters of the whole SC. Furthermore, Simulation is also common, as it can represent in a certain realistic way the system's features and flows of donors, blood products and information throughout the whole SC [9]. Yet, recent publications tend combine simulation with mathematical optimization to address BSC problems, which offers a way of handling the complexity inherent in each stage of the network by enhancing the possibilities of making practical improvements [2,9].

3.5. Main decisions, challenges and objectives

Modelling the BSC involves: 1) a complex decision-making process; 2) several constraints; 3) sources of uncertainty; and 4) multiple and conflicting objectives.

Figure 1 presents the main BSC problems and planning decisions, organized by stage and aligned with the 3 main hierarchical decision levels, from the reviewing of the works by Torrado & Barbosa-Póvoa (2022) and Meneses et al. (2022). The main problems are in the colorful boxes, and the bullet points below each colorful box identify the decisions carried by each problem.

During the decision-making process several challenges come in the way, which are the constraints faced by the BSC management. Meneses et al. (2022), besides developing a conceptual model for each BSC management problem, present an innovative modelling framework to address the planning of the BSC, for the strategic and tactical planning levels, reviewing existing models from literature and identifying the key clusters and constraints identified in literature to model the main BSC planning decisions, as illustrated in figure 2.

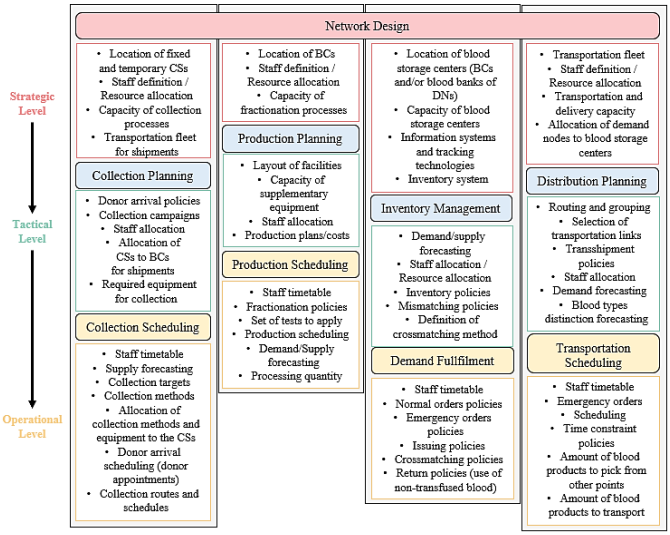

Fig. 1: The BSC main management problems and decisions by stage and hierarchical decision level [9,11,21].

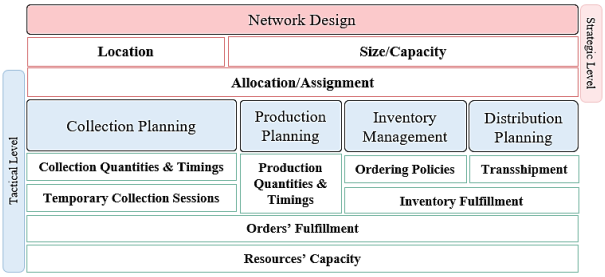

Fig. 2: Strategic and tactical constraints of the BSC management [10,20].

The BSC is also characterized for its risks and uncertainties, challenging the design and management of the BSC network. Due to the voluntary donors' uncertain behavior, there is an uncertain quantity, quality and arrival time of new blood, and given patients' uncertain needs, there is an uncertain quantity of blood products needed at the DNs, along with the patients' respective blood types. Subsequently, the uncertain demand contributes to an uncertain quantity of blood products to be produced and distributed. Consequently, these uncertainties end up contributing to the wastage or shortage of blood.

At last, managing the BSC involves multiple objectives. The most frequent objectives found are the total cost minimization followed by wastage minimization [9,10]. Additionally, aligned with the 3 sustainability dimensions, most reviews are focused on the Economic pillar (minimizing total costs), then on the Social pillar (maximizing social effects), and few considered the Environmental pillar (minimizing environmental impacts) [20].

4. Perishable supply chains

To find similarities with the BSC and determine which findings can be applied to the BSC to overcome the identified challenges, SC management for other perishable products was reviewed.

A product is perishable if during the considered planning period at least one of these conditions takes place: 1) its physical status worsens noticeably, by spoilage, decay, depletion or other; 2) its value decreases in the customers' perception; 3) there is a danger of a future reduced functionality, based in some authority's opinion [21]. So, the perishability of products is a tremendous challenge for building sustainable and efficient SCs. There are two types of perishable products: the ones with a fixed SL and the ones with a stochastic SL [21]. The first relates to products with a well-defined expiry date, beyond which they must be discarded, such as food, pharmaceutical and biological products (blood). The second are those whose lifespan is not predetermined and their deterioration occurs over time and the products gradually lose their value until they become non-consumable, such as fresh foods or bread [21,22].

The Agro-food Supply Chain (AFSC) is characterized by frequent customer orders of small quantities, tight delivery time windows, production and demand uncertainty and the products' perishability [22]. Hence, it is further analyzed due to its importance and the existence of a more extensive literature search on this topic in comparison to the BSC. Mirabelli & Solina (2022) presents a literature review of 54 papers published from 2005 to 2020 on the integrated management of perishable SCs, with the goal to highlight the most used approaches to address perishability and limit food waste, in order to make SCs more sustainable. Is concluded that, due to its growing importance and relevance, this topic has been considerably studied in literature in recent years and academic interest in models capable of jointly optimizing production, storage and distribution of perishable products has been growing.

4.1. The agro-food supply chain

A general AFSC, as illustrated in figure 3, is characterized by five operational echelons, supporting product flows, financial flows, information flows and energy and natural resources' flows [23,24]. Following this, an AFSC comprises a set of activities in a "farm-to-fork" sequence, as presented in figure 3. Just like for the blood, agri-products are characterized by their uniqueness, heterogeneity and perishability, so the AFSC also exhibits specific characteristics that raise the need for special managerial capabilities [25].

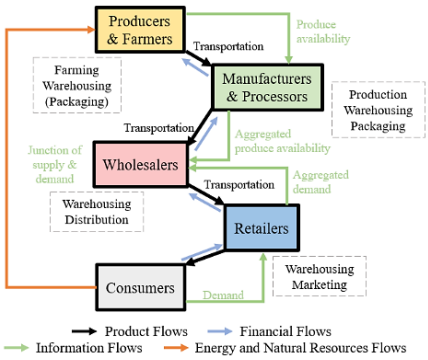

Fig. 3: The AFSC [23,24].

Esteso et al. (2018) present a conceptual framework and state of the art on designing the AFSC through mathematical programming modelling, considering the SC's inherent characteristics, decisions, objectives, constraints and sources of uncertainty. The authors propose 7 strategic decisions for designing the SC, as well as 9 tactical and operational decisions, exposed while designing the network, mentioned as the planning decisions. Additionally, this conceptual framework is restricted to the work of Tsolakis et al. (2014), which provide a taxonomy of existing efforts in the reviewed literature up to 2014, mapped on the same main hierarchical decision levels – strategic and tactical & operational decisions. Figure 4 presents the designing and planning decisions proposed by works.

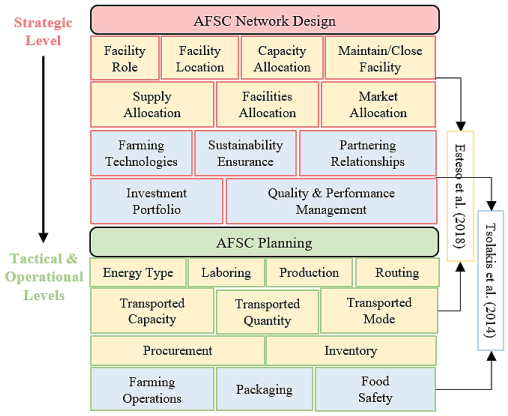

Fig. 4: The AFSC management decisions [24,25].

During the decision-making process represented in figure 4, several challenges are faced, which limit the decision-maker(s) power of decision. When modelling the problem, these challenges translate into the constraints that restrict the model with the real-life challenges faced by the SC, as presented in figure 5. The uncertain parameters in the AFSC relate to the products, the processes, the market and the environment, and are also presented and detailed in figure 5.

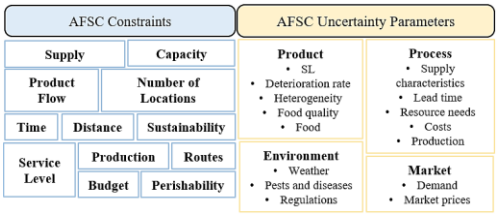

Fig. 5: The AFSC clusters of constraints and uncertainty parameters [25].

Regarding the optimization criteria in AFSC models, mathematical programming models used for this SC can have one or multiple different objectives related to different subjects, such as sustainability or economy. A SC is Sustainable when it considers economic, environmental and social aspects. If only environmental and economic aspects are considered it is called a Green SC, and in case only economic aspects are considered then it is called a Lean SC [26]. According to Esteso et al. (2018), most models design Lean SCs, while Green and Sustainable SCs are less considered. All models pursue economic objectives (minimization of costs or maximization of profits). Social objectives are less pursued (minimizing total delivery times, maximizing customer satisfaction, maximizing product quality, job creation or the conditional value-at-risk of customer services). Environmental objectives (minimizing CO_2 emissions, water usage or waste), are even less addressed.

4.2. Agro-food supply chain transfers to the blood supply chain

The AFSC is very similar to the BSC, namely when it comes to the products' characteristics. Perishability is possibly the most important and common characteristic between the two types of products, that makes the two SCs complex and related, as both have limited SLs and each type of product has its own specific storage requirements. Given the similarities between the AFSC and the BSC decision-making processes, AFSC constraints are applicable to the BSC, especially regarding blood products and blood-related processes and activities. As for the SC's uncertainties, the four clusters of uncertain parameters presented at figure 5 are obviously directed to the AFSC, but some can be comparable with the BSC uncertainties. Regarding the optimization criteria, the models for the AFSC and for the BSC have very similar objectives, as the minimization of total costs is usually the main goal for both SCs and both SCs target economic, social and environmental objectives, to achieve sustainability.

Therefore, methods from the AFSC are explored for the BSC, particularly from Singh et al. (2018) and Qi & Hu (2020), which presented interesting insights from the AFSC that can be applied to the BSC. The incorporation of these innovations is what is going to be explored in this work's model, mainly to understand if it is optimal for reducing wastage of blood units in the BSC.

5. Mathematical model

5.1. Problem definition

For the formulated model in this work, each blood product managed throughout the BSC, besides having a specific SL, has a maximum age for each DN, which is the maximum age for which the blood products at the DNs can be transfused to their patients. Hence, blood products in storage at the DNs with ages older than the DNs' respective maximum age for that product, are not going to be transfused and therefore are returned to the BC for the possibility to be redistributed to other DNs. The FIFO policy is adopted both for the (re)distribution and transfusion, so the returned units from the DNs to the BC, if suited for other DN, are (re)distributed first, and their wastage is avoided, since at the DNs these are also transfused first. Thus, the model is mainly focused on minimizing waste, through the redistributions, and increasing the quality of transfusions, through the introduction of a maximum age of transfusions at each DN.

(Re)Distribution:

- At the 1st time period, there are no (re)distributions, only transfusions at the DNs. This activity only happens for the 1st time at the 2nd time period, according to the ordered quantities by the DNs at the end of the 1st time period.
- Blood units are sent to the DNs from the BC at the start of each time period (except the 1st), according to the FIFO policy, the ordered quantities by the DNs, the DNs' maximum ages of blood products and the units' Service Distance Requirements [27].
- The DNs send back blood units to the BC with ages older than each DN's maximum age, to be redistributed to other DNs at the following time period, if the age of the units is still suited for other DNs.
- For each travel, fuel and refrigeration costs are calculated, according to the load of the vehicles and the driving times and distances to the DNs [28].

Inventory management at the BC:

- The BC is initially empty, with no units in inventory. Thus, there is no waste at the 1st time period, at the BC.
- The inventory levels of the BC depend on the daily supply from collection and production, on the (re)distributed units to the DNs and on the returned units from the DNs.
- Wasted units: if units in storage surpass the respective SL, then these are wasted, and wastage costs are accounted.
- Unmet demand: if the BC's inventory is not enough to meet the demand of the DNs, then unmet demand costs are accounted.
- The FIFO policy is followed for the (re)distribution of blood to the DNs, to prioritize the utilization of the older and returned units from other DNs.
- At the end of each time period, the BC receives the blood orders from the DNs, to be provided at the start of the following period.

Inventory management at the DNs:

- First inventory update: at the start of each time period (except for the 1st one), the DNs receive and return blood units, and the inventory is updated for the first time.
- Wasted units: if units in storage surpass the respective SL, then these are wasted, and wastage costs are accounted.
- Transfusions and unmet demand: according to the DNs' maximum age of blood products and patients' demands, following the FIFO policy, blood products are used for transfusions, and, if the DNs' inventory is not enough to meet patients' demands, then unmet demand costs are accounted.
- Second inventory update, after the transfusions.
- Discarded units: if the maximum inventory level for a blood product of a certain blood type is reached, then, according to the FIFO policy, the extra units must be discarded, and disposal costs are accounted.
- Safety stock units: if the minimum inventory level for a blood product of a certain blood type is reached, then safety stock utilization costs are accounted, and the number of units needed to restore the minimum inventory is added in next period's orders.
- Final inventory update, according to the discarded units.
- Blood orders: at the end of each time period, the DNs send blood orders to the BC, according to that time period's demand, the remaining available inventory and the safety stock units used.

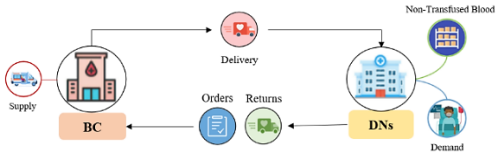

Fig. 6: Conceptual model.

5.2. Model formulation

5.2.1. Notation

- **Sets**

A	ages, $a \in A$
D	DNs, $d \in D$
$P1$	blood products, $p1 \in P1$
$P2$	blood types, $p2, p2' \in P2$
T	time periods, $t \in T$

- **Input parameters**

$CBSubsDN_{p1}$	Baseline substitution cost for blood product $p1$ at transfusions at DN d (then, as according to the priority matrix, the least favorable substitutions are more expensive).
$CBSubs_{p1}$	Baseline substitution cost for blood product $p1$ at (re)distribution (then, as according to the priority matrix, the least favorable substitutions are more expensive).

$CDis_{p1,p2}$ Baseline disposal cost per blood product $p1$ of type $p2$, at the BC (the actual disposal cost is calculated by dividing this baseline cost by the age of each unit, so discarding younger units results in greater costs and thus older units are disposed first).

$CFuel_{e(f)}$ Fuel consumption cost per unit distance of the distribution vehicles when no load (full load).

$CPQt^t_{p1,p2}$ Supply of blood product $p1$ of type $p2$ at the BC, with 0 days of age, at time period t.

$CRefriBCDN_{p1}$ Refrigeration cost per unit of blood product $p1$, at the BC and the DNs.

$CRefri_{p1}$ Refrigeration cost per unit of blood product $p1$, in transit, on the distribution vehicles.

$CRefri_u$ Cooling cost per discharge when unloading.

$CShort_{p1,p2}$ Shortage cost, per blood product $p1$ of type $p2$, at the BC and the DNs.

$CSS_{p1,p2}$ Cost per unit of blood product $p1$ of type $p2$ used from the safety stock for transfusions, at the DNs.

$CW_{p1,p2}$ Wastage cost, per blood product $p1$ of type $p2$.

$DemQt^t_{d,p1,p2}$ Demanded quantity of blood product $p1$ of type $p2$, at time period t, at DN d.

$Dist_d$ Driving distance between the BC and DN d.

$Dist_{max}$ Maximum driving distance (between the BC and the farthest DN).

$InvAux^0_{d,p1,p2,a}$ Initial inventory level of blood product $p1$ of type $p2$ with age a, at DN d, before meeting patients' demands.

$InvMax_{d,p1,p2}$ Maximum inventory level for blood product $p1$ of type $p2$, at DN d.

$MaxAge_{d,p1}$ Maximum age requested for ordered and demanded blood product $p1$ at DN d.

$MaxCap$ Maximum storage capacity of the BC.

$MaxCap_d$ Maximum storage capacity of DN d.

$MaxL$ Maximum load of the distribution vehicles.

$MComp_{p2,p2'}$ Compatibility matrix between blood types (equals 1 if the demand for blood type $p2'$ can be satisfied with blood type $p2$, equals 0 otherwise).

$MSubs_{p2,p2'}$ Priority substitution auxiliary matrix between blood types (in case the demand for blood type $p2'$ can be satisfied with blood type $p2$, $MSubs_{p2,p2'}$ can take values between 1 and 1/7, representing the least favorable and the most favorable substitutions, respectively).

SL_{p1} SL of blood product $p1$.

$SS_{d,p1,p2}$ Minimum inventory (safety stock), at DN d, for blood product $p1$ of type $p2$.

T_d Driving time between the BC and DN d.

- **Auxiliar decision expressions**

$Dis^t_{d,p1,p2}$ Auxiliar parameter for the quantity of discarded units of blood product $p1$ of type $p2$, due to overtaking the respective maximum inventory level, at DN d.

$Fuel^t_d$ Fuel consumption when driving from the BC to DN d and back, at time period $t \geq 1$.

$InvAux2^t_{d,p1,p2,a}$ Auxiliary parameter for the inventory update at DN d, of blood product $p1$ of type $p2$ with age a, at time period t, after meeting patients' demand.

$InvAux^t_{d,p1,p2,a}$ Auxiliary parameter for the inventory update at DN d, of blood product $p1$ of type $p2$ with age a, at time period $t \geq 1$, after the (re)distribution of blood units and before meeting patients' demands.

$Inv^t_{d,p1,p2}$ Total inventory level of blood product $p1$ of type $p2$, at time period t, at DN d, after that period's transfusions to meet demand.

$Inv^t_{p1,p2}$ Total inventory level of blood product $p1$ of type $p2$, at time period t, at the BC.

$L1(2)^t_d$ Load of vehicle when driving from the BC (DN d) to DN d (BC), at time period $t \geq 1$.

$LR1(2)^t_d$ Load rate of vehicle when driving from the BC (DN d) to DN d (BC), at time period $t \geq 1$.

$OrdQt^t_{d,p1,p2}$ Ordered quantity, at time period t, of blood product $p1$ of blood type $p2$ by DN d.

$RefriBC(DN)^t$ Refrigeration cost for storage at the BC (DNs), at time period t.

$RefriDrv1(2)^t_d$ Refrigeration cost when driving from the BC (DN d) to DN d (BC), at time period $t \geq 1$.

$RefriUn^t_d$ Refrigeration cost of unloading blood units at DN d, at time period $t \geq 1$.

$SDR^t_{d,p1,p2,a}$ Service Distance Requirement from the BC to DN d, at time period $t \geq 1$, for the transport of blood product $p1$ of type $p2$ in case its age is lower than the maximum age requested and demanded for DN d.

$SS^t_{d,p1,p2}$ Auxiliar parameter for the quantity of blood product $p1$ of type $p2$ from the safety stock of DN d, at time period t.

$S^t_{d,p1,p2,a}$ Service level parameter for (re)distribution to DN d, at time period $t \geq 1$, of units of blood product $p1$ of type $p2$ with age a (equals 1 if the actual distance is equal or lower than the SDR, equals 0 otherwise).

$UDemDN^t_{d,p1,p2}$ Unmet demand of blood product $p1$ of blood type $p2$, at time period t, at DN d.

$UDem^t_{d,p1,p2}$ Unmet demand of blood product $p1$ of blood type $p2$, at time period $t \geq 1$, for DN d.

$UDem^t_{p1,p2}$ Unmet demand of blood product $p1$ of blood type $p2$, at time period $t \geq 1$, at the BC.

$WQt^t_{d,p1,p2}$ Wasted quantity of blood product $p1$ of type $p2$, at time period t, at DN d.

$WQt^t_{p1,p2}$ Wasted quantity of blood product $p1$ of type $p2$, at time period $t \geq 1$, at the BC.

- **Decision variables**

$c^t_{d,p1,p2}$ Binary variable for the total quantity of discarded units of blood product $p1$ of type $p2$, at DN d, at time period t.

$dqt^t_{d,p1,p2,a}$ Integer variable for the quantity of discarded units of blood product $p1$ of type $p2$ with age a, at time period t, due to overtaking its maximum inventory level, at DN d.

$inv^t_{d,p1,p2,a}$ Integer variable for the inventory level of blood product $p1$ of blood type $p2$ with age a, at time period $t \geq 1$, at DN d.

$inv^t_{p1,p2,a}$ Integer variable for the inventory level of blood product $p1$ of type $p2$ with age a, at time period t, at the BC.

$p^t_{d,p1,p2,a}$ Binary variable for visiting DN d for (re)distributing units of blood product $p1$ of type $p2$ with age a, at time period t.

$qDN^t_{d,p1,p2,a}$ Integer variable for the quantity of blood product $p1$ of type $p2$ with age a used to meet the respective product's demand at DN d, at time period t.

$qt^t_{d,p1,p2,a}$ Integer variable for the quantity of blood product $p1$ of type $p2$ with age a (re)distributed to DN d, at time period t.

$rqt^t_{d,p1,p2,a}$ Integer variable for the quantity of blood product $p1$ of type $p2$ with age a to return to the BC from DN d, at time period t.

$s^t_{d,p1,p2}$ Binary variable for the quantity of blood product $p1$ of type $p2$ used from the safety stock of DN d for transfusions, at time period t.

$sDN^t_{d,p1,p2',p2,a}$ Integer variable for the quantity of blood product $p1$ of type $p2'$ with age a used to meet demand of blood product $p1$ of blood type $p2$, at DN d, at time period t.

$sqt^t_{d,p1,p2,p2',a}$ Integer variable for the quantity of blood product $p1$ of type $p2$ with age a transported to DN d, used to substitute blood type $p2'$, at time period t.

$u^t_{d,p1,p2}$ Binary variable for DN d ordered quantities of blood product $p1$ of type $p2$, at time period t.

$v^t_{d,p1,p2,a}$ Binary variable for visiting DN d for the return of units of blood product $p1$ of type $p2$ with age a, at time period t.

5.2.2. Constraints

Initial inventory update, at the BC:

$$inv^t_{p1,p2,0} = CPQt^t_{p1,p2}, \ \forall\, t, \forall\, p1, \forall\, p2 \quad (1)$$

$$inv^t_{p1,p2,a} = inv^{t-1}_{p1,p2,a-1} + \sum_d (v^t_{d,p1,p2,a} \times rqt^t_{d,p1,p2,a} - p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a})), \ \forall\, t \geq 1, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq SL_{p1} \quad (2)$$

Wasted quantities, at the BC:

$$WQt^t_{p1,p2} = \sum_{a \geq SL_{p1}} inv^{t-1}_{p1,p2,a}, \ \forall\, t \geq 1, \forall\, p1, \forall\, p2 \quad (3)$$

Total inventory update, at the BC:

$$Inv^t_{p1,p2} = \sum_{a=0}^{SL_{p1}} inv^t_{p1,p2,a}, \ \forall\, t, \forall\, p1, \forall\, p2 \quad (4)$$

Available inventory for (re)distribution to the DNs:

$$qt^t_{d,p1,p2,a} \leq inv^{t-1}_{p1,p2,a-1}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq MaxAge_{d,p1} \quad (5)$$

$$sqt^t_{d,p1,p2,p2',a} \leq MComp_{p2,p2'} \times inv^{t-1}_{p1,p2,a-1}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, 1 \leq a \leq MaxAge_{d,p1} \quad (6)$$

Available inventory at each DN for returning to the BC:

$$rqt^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, MaxAge_{d,p1} + 1 \leq a \leq SL_{p1} \quad (7)$$

Relation between ordered units from the DNs and (re)distributed units from the BC:

$$\sum_{a=1}^{MaxAge_{d,p1}} (p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a})) \leq u^{t-1}_{d,p1,p2} \times OrdQt^{t-1}_{d,p1,p2}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2 \quad (8)$$

Unmet demand of the BC:

$$UDem^t_{d,p1,p2} = u^{t-1}_{d,p1,p2} \times OrdQt^{t-1}_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}} (p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a})), \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2 \quad (9)$$

$$UDem^t_{p1,p2} = \sum_d UDem^t_{d,p1,p2}, \ \forall\, t \geq 1, \forall\, p1, \forall\, p2 \quad (10)$$

Initial inventory update, at the DNs:

$$InvAux^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1} + p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a}), \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq MaxAge_{d,p1} \quad (11)$$

$$InvAux^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1} - v^t_{d,p1,p2,a} \times rqt^t_{d,p1,p2,a}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, MaxAge_{d,p1} + 1 \leq a \leq SL_{p1} \quad (12)$$

$$InvAux^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1}, \ \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq SL_{p1} + 1 \quad (13)$$

Wasted quantities, at the DNs:

$$WQt^t_{d,p1,p2} = \sum_{a \geq SL_{p1}+1} InvAux^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2 \quad (14)$$

Available inventory, at the DNs, for transfusions:

$$qDN^t_{d,p1,p2,a} \leq InvAux^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq MaxAge_{d,p1} \quad (15)$$

$$sDN^t_{d,p1,p2',p2,a} \leq MComp_{p2',p2} \times InvAux^t_{d,p1,p2',a},\ \forall t, \forall d, \forall p1, \forall p2, \forall p2', \forall 1 \leq a \leq MaxAge_{d,p1} \quad (16)$$

Inventory update after transfusions, at the DNs:

$$InvAux2^t_{d,p1,p2,a} = InvAux^t_{d,p1,p2,a} - qDN^t_{d,p1,p2,a} - \sum_{p2'} sDN^t_{d,p1,p2,p2',a},\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq MaxAge_{d,p1} \quad (17)$$

$$InvAux2^t_{d,p1,p2,a} = InvAux^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2, \forall a \geq MaxAge_{d,p1} + 1 \quad (18)$$

Discarded units of blood, at the DNs:

$$Dis^t_{d,p1,p2} = \sum_{a=1}^{SL_{p1}} (InvAux2^t_{d,p1,p2,a}) - InvMax_{d,p1,p2},\ \forall t, \forall d, \forall p1, \forall p2 \quad (19)$$

$$\sum_{a=1}^{SL_{p1}} dqt^t_{d,p1,p2,a} = c^t_{d,p1,p2} \times Dis^t_{d,p1,p2},\ \forall t, \forall d, \forall p1, \forall p2 \quad (20)$$

Maximum inventory levels, at the DNs:

$$\sum_{a=1}^{SL_{p1}} InvAux2^t_{d,p1,p2,a} \leq InvMax_{d,p1,p2},\ \forall t, \forall d \quad (21)$$

Final inventory update, at the DNs:

$$inv^t_{d,p1,p2,a} = InvAux2^t_{d,p1,p2,a} - dqt^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq SL_{p1} \quad (22)$$

Safety stock units, at the DNs:

$$SS^t_{d,p1,p2} = SS_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}} inv^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2 \quad (23)$$

$$SS\_Units^t_{d,p1,p2} = s^t_{d,p1,p2} \times SS^t_{d,p1,p2},\ \forall t, \forall d, \forall p1, \forall p2 \quad (24)$$

Total inventory update, at the DNs:

$$Inv^t_{d,p1,p2} = \sum_{a=1}^{SL_{p1}} inv^t_{d,p1,p2,a},\ \forall t, \forall d, \forall p1, \forall p2 \quad (25)$$

Ordered quantities, by the DNs:

$$OrdQt^t_{d,p1,p2} = DemQt^t_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}-1} (inv^t_{d,p1,p2,a}) + s^t_{d,p1,p2} \times SS^t_{d,p1,p2},\ \forall t, \forall d, \forall p1, \forall p2 \quad (26)$$

Relation between demand and transfused units:

$$\sum_{a=1}^{MaxAge_{d,p1}} (qDN^t_{d,p1,p2,a} + \sum_{p2'} sDN^t_{d,p1,p2',p2,a}) \leq DemQt^t_{d,p1,p2},\ \forall t, \forall d, \forall p1, \forall p2 \quad (27)$$

Unmet Demand, at the DNs:

$$UDemDN^t_{d,p1,p2} = DemQt^t_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}} (qDN^t_{d,p1,p2,a} + \sum_{p2'} sDN^t_{d,p1,p2',p2,a}),\ \forall t, \forall d, \forall p1, \forall p2 \quad (28)$$

Service distance requirement for (re)distributed blood units:

$$SDR^t_{d,p1,p2,a} = (MaxAge_{d,p1} + 1 - a) \times \frac{Dist_d}{T_d},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (29)$$

$$S^t_{d,p1,p2,a} = \begin{cases} Dist_d,\ if\ Dist_d \leq SDR^t_{d,p1,p2,a} \\ 0,\ otherwise \end{cases},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (30)$$

Constraints for the binary variables:

$$v^t_{d,p1,p2,a} \times MaxCap \geq rqt^t_{d,p1,p2,a},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (31)$$

$$p^t_{d,p1,p2,a} \times Dist_{max} \geq S^t_{d,p1,p2,a},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (32)$$

$$u^t_{d,p1,p2} \times OrdQt^t_{d,p1,p2} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2 \quad (33)$$

$$c^t_{d,p1,p2} \times Dis^t_{d,p1,p2} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2 \quad (34)$$

$$SS^t_{d,p1,p2} \times (s^t_{d,p1,p2} - 1) \geq 0,\ \forall t, \forall d, \forall p1, \forall p2 \quad (35)$$

Loads of vehicles, load rates and fuel consumption:

$$L1^t_d = \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} \left(p^t_{d,p1,p2,a} \times \left(qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a}\right)\right),\ \forall t \geq 1, \forall d \quad (36)$$

$$L2^t_d = \sum_{p1} \sum_{p2} \sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (v^t_{d,p1,p2,a} \times rqt^t_{d,p1,p2,a}),\ \forall t \geq 1, \forall d \quad (37)$$

$$L1(2)^t_d \leq MaxL,\ \forall t \geq 1, \forall d \quad (38)$$

$$LR1(2)^t_d = \frac{L1(2)^t_d}{MaxL},\ \forall t \geq 1, \forall d \quad (39)$$

$$Fuel^t_d = CFuel_e + LR1^t_d \times (CFuel_f - CFuel_e) + LR2^t_d \times (CFuel_f - CFuel_e),\ \forall t \geq 1, \forall d \quad (40)$$

Refrigeration costs:

$$RefriBC^t = \sum_{p1} \sum_{p2} (Inv^t_{p1,p2} \times CRefriBCDN_{p1}),\ \forall t \quad (41)$$

$$RefriDN^t = \sum_d \sum_{p1} \sum_{p2} (Inv^t_{d,p1,p2} \times CRefriBCDN_{p1}),\ \forall t \quad (42)$$

$$RefriDrv1^t_d = T_d \times \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} (p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a}) \times CRefri_{p1}),\quad \forall t \geq 1, \forall d \quad (43)$$

$$RefriDrv2^t_d = T_d \times \sum_{p1} \sum_{p2} \sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (v^t_{d,p1,p2,a} \times rqt^t_{d,p1,p2,a} \times CRefri_{p1}),\ \forall t \geq 1, \forall d \quad (44)$$

$$RefriUn^t_d = \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} (p^t_{d,p1,p2,a} \times (qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2',p2,a}) \times CRefri_u),\ \forall t \geq 1, \forall d \quad (45)$$

Decision variables' domains:

$$inv^0_{p1,p2,a} = 0,\ \forall p1, \forall p2, \forall 1 \leq a \leq SL_{p1} \quad (46)$$

$$inv^t_{p1,p2,a} \geq 0,\ \forall t \geq 1, \forall p1, \forall p2, \forall 1 \leq a \leq SL_{p1} \quad (47)$$

$$inv^t_{p1,p2,a} = 0,\ \forall t, \forall p1, \forall p2, \forall a \geq SL_{p1} + 1 \quad (48)$$

$$inv^t_{p1,p2,0} \geq 0,\ \forall t, \forall p1, \forall p2 \quad (49)$$

$$qt^t_{d,p1,p2,a} \geq 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq MaxAge_{d,p1} \quad (50)$$

$$qt^t_{d,p1,p2,a} = 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq MaxAge_{d,p1} + 1 \quad (51)$$

$$qt^0_{d,p1,p2,a} = 0,\ \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (52)$$

$$sqt^t_{d,p1,p2,p2',a} \geq 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall p2', \forall 1 \leq a \leq MaxAge_{d,p1} \quad (53)$$

$$sqt^t_{d,p1,p2,p2',a} = 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall p2', \forall a \geq MaxAge_{d,p1} + 1 \quad (54)$$

$$sqt^0_{d,p1,p2,p2',a} = 0,\ \forall d, \forall p1, \forall p2, \forall p2', \forall a \geq 1 \quad (55)$$

$$p^0_{d,p1,p2,a} = 0,\ \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (56)$$

$$p^t_{d,p1,p2,a} \in \{0,1\},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (57)$$

$$inv^t_{d,p1,p2,a} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq SL_{p1} \quad (58)$$

$$inv^t_{d,p1,p2,a} = 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall a \geq SL_{p1} + 1 \quad (59)$$

$$inv^t_{d,p1,p2,0} = 0,\ \forall t, \forall d, \forall p1, \forall p2 \quad (60)$$

$$qDN^t_{d,p1,p2,a} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq MaxAge_{d,p1} \quad (61)$$

$$qDN^t_{d,p1,p2,a} = 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall a \geq MaxAge_{d,p1} + 1 \quad (62)$$

$$sDN^t_{d,p1,p2,p2',a} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall p2', \forall 1 \leq a \leq MaxAge_{d,p1} \quad (63)$$

$$sDN^t_{d,p1,p2,p2',a} = 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall p2', \forall a \geq MaxAge_{d,p1} + 1 \quad (64)$$

$$dqt^t_{d,p1,p2,a} \geq 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq SL_{p1} \quad (65)$$

$$dqt^t_{d,p1,p2,a} = 0,\ \forall t, \forall d, \forall p1, \forall p2, \forall a \geq SL_{p1} + 1 \quad (66)$$

$$c^t_{d,p1,p2} \in \{0,1\},\ \forall t, \forall d, \forall p1, \forall p2 \quad (67)$$

$$u^t_{d,p1,p2} \in \{0,1\},\ \forall t, \forall d, \forall p1, \forall p2 \quad (68)$$

$$rqt^t_{d,p1,p2,a} = 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall 1 \leq a \leq MaxAge_{d,p1} \quad (69)$$

$$rqt^t_{d,p1,p2,a} \geq 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall MaxAge_{d,p1} + 1 \leq a \leq SL_{p1} \quad (70)$$

$$rqt^t_{d,p1,p2,a} = 0,\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq SL_{p1} + 1 \quad (71)$$

$$rqt^0_{d,p1,p2,a} = 0,\ \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (72)$$

$$v^0_{d,p1,p2,a} = 0,\ \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (73)$$

$$v^t_{d,p1,p2,a} \in \{0,1\},\ \forall t \geq 1, \forall d, \forall p1, \forall p2, \forall a \geq 1 \quad (74)$$

$$s^t_{d,p1,p2} \in \{0,1\},\ \forall t, \forall d, \forall p1, \forall p2 \quad (75)$$

5.2.3. Objective Function

The objective function englobes the minimization of all the costs related with the mentioned BSC characteristics. Hence, the model tries to generate a positive impact on sustainability, not only by reducing the wastage and disposal of blood units along the BSC, but by pursuing multiple objectives that relate to the three main sustainability aspects: economic (by minimizing total costs), social (by minimizing substitution and shortage costs) and environmental (by minimizing wastage, disposal, refrigeration and fuel costs). Moreover, this model follows the FIFO policy at the level of blood distribution and at the level of blood transfusion, so the objective function also englobes the modelling for the FIFO policies.

Wastage costs:

$$WasteCosts^0 = \sum_d \sum_{p1} \sum_{p2} (CW_{p1,p2} \times WQt^0_{d,p1,p2}) \quad (76)$$

$$WasteCosts^t = \sum_{p1} \sum_{p2} (CW_{p1,p2} \times WQt^t_{p1,p2}) + \sum_d \sum_{p1} \sum_{p2} (CW_{p1,p2} \times WQt^t_{d,p1,p2}),\ \forall t \geq 1 \quad (77)$$

Substitution costs:

$$SubsCosts^0 = \sum_d \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} \sum_{p2'} (sDN^0_{d,p1,p2,p2',a} \times CBSubsDN_{p1} \times MSubs_{p2,p2'}) \quad (78)$$

$$SubsCosts^t = \sum_d \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} \sum_{p2'} (sqt^t_{d,p1,p2,p2',a} \times CBSubs_{p1} \times MSubs_{p2,p2'} + sDN^t_{d,p1,p2,p2',a} \times CBSubsDN_{p1} \times MSubs_{p2,p2'}),\ \forall t \geq 1 \quad (79)$$

Disposal costs:

$$DisCosts^t = \sum_d \sum_{p1} \sum_{p2} \sum_{a=1}^{SL_{p1}} (dqt^t_{d,p1,p2,a} \times \frac{CDis_{p1,p2}}{a}),\quad \forall t \quad (80)$$

Shortage costs:

$$ShortCosts^0 = \sum_d \sum_{p1} \sum_{p2} \left(CShort_{p1,p2} \times UDemDN^0_{d,p1,p2}\right) \quad (81)$$

$$ShortCosts^t = \sum_{p1} \sum_{p2} \left(CShort_{p1,p2} \times UDem^t_{p1,p2}\right) + \sum_d \sum_{p1} \sum_{p2} \left(CShort_{p1,p2} \times UDemDN^t_{d,p1,p2}\right), \ \forall\, t \geq 1 \quad (82)$$

Safety stock costs:

$$SSCosts^t = \sum_d \sum_{p1} \sum_{p2} (SS\_Units^t_{d,p1,p2} \times CSS_{p1,p2}), \quad \forall\, t \quad (83)$$

Fuel costs:

$$FuelCosts^t = \sum_d (Dist_d \times Fuel^t_d), \ \forall\, t \geq 1 \quad (84)$$

Refrigeration costs:

$$RefriCosts^0 = RefriBC^0 + RefriDN^0 \quad (85)$$

$$RefriCosts^t = RefriBC^t + RefriDN^t + \sum_d (RefriDrv1^t_d + RefriUn^t_d + RefriDrv2^t_d), \quad \forall\, t \geq 1 \quad (86)$$

FIFO policy – (Re)distributions:

$$DistrFIFO^t = \sum_d \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} \left((qt^t_{d,p1,p2,a} + \sum_{p2'} sqt^t_{d,p1,p2,p2',a}) \times \frac{MaxAge_{d,p1}}{a}\right), \ \forall\, t \geq 1 \quad (87)$$

FIFO policy – Transfusions:

$$TransfFIFO^t = \sum_d \sum_{p1} \sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} \left((qDN^t_{d,p1,p2,a} + \sum_{p2'} sDN^t_{d,p1,p2,p2',a}) \times \frac{MaxAge_{d,p1}}{a}\right), \ \forall\, t \quad (88)$$

Objective function:

$$Min(WasteCosts^0 + SubsCosts^0 + DisCosts^0 + ShortCosts^0 + SSCosts^0 + RefriCosts^0 + TransfFIFO^0 + \sum_{t \geq 1} (WasteCosts^t + SubsCosts^t + DisCosts^t + ShortCosts^t + SSCosts^t + FuelCosts^t + RefriCosts^t + DistrFIFO^t + TransfFIFO^t) \quad (89)$$

It is important to mention that the previously described model is formulated as a Mixed Integer Non-Linear Programming model, with various non-linear constraints, since multiplying two variables is quite often the most straightforward way of writing constraints. Given the complexity of solving models of this nature, the model was linearized and the non-linear constraints were reformulated in order to transform the model into a Mixed Integer Linear Programming model.

6. Results and discussion

6.1. Data and assumptions

This model is to be applied for the Portuguese case, as presented in chapter 2, particularly for the CSTL and the DNs from its region of operation, using the supply and demand data from December of 2019, the last month with official IPST data. The goal is to minimize blood wastage, particularly for pools of PLTs with PR which have been considerably wasted in the previous years, to counter the insufficient local supply, which are unfortunately critical downsides from the Portuguese Southern Region's BSC, as well as to increase the quality of service by reducing the average age of transfused units at the DNs.

The initial parameters, such as the costs, inventory levels and maximum storage capacities, as well as the BC and the DNs, are explored from IPST's sources as far as possible. However, there is limited official information on specific parameters for the Portuguese BSC, meaning that some of them are retrieved from literature and then adapted to remain consistent to the Portuguese BSC.

For the wastage, disposal, shortage and safety stock costs, it is assumed an order of preference between the blood types according to their possible compatibilities and priorities in substitutions (O-, B-, A-, O+, AB-, B+, A+ and AB+, from most to least expensive), so each blood type has a different cost. As for the DNs, the approximate driving distances and times from the BC to each DN were calculated using *Google Maps*. As for the maximum age of PLTs for transfusions at each DN, there is no official information and it is initially assumed that most of the considered DNs transfuse PLTs up to the end of their respective SL, which is of 7 days [9]. Hence, considering that the fresher the transfused blood the less risk of contamination and negative effects on patients and the possibility of redistributing blood, to differentiate the DNs it was assumed that DNs specialized in oncology require a lower maximum age and that DNs with a wider range of medical specialties and emergency services have a higher maximum age. Regarding the demand and supply levels, IPST provide data on the daily number of various blood products distributed from the CSTs to the DNs and the daily number of WB collected at the CSTs. Hence, data from December of 2019 and the previous months was used to obtain the demand and supply levels for the 5 considered DNs, for December of 2019. The minimum inventory levels of the DNs were obtained through IPST recommendations, as well as the satisfactory inventory levels of the DNs, which were used as the initial inventory levels of the DNs. The maximum inventory levels were assumed the same as the ones by Meneses (2019).

Tables 2, 3 and 4 present the input parameters used.

Table 2: Wastage, disposal, shortage and safety stock costs, for pools of PLTs with PR, per blood type.

p1 = PLTs	p2 = O-	p2 = O+	p2 = A-	p2 = A+	p2 = B-	p2 = B+	p2 = AB-	p2 = AB+
$CW_{p1,p2}$ (€/unit)	102	72	82	42	92	52	62	32
$CDis_{p1,p2}$ (€/unit)	152	122	132	92	142	102	112	82
$CShort_{p1,p2}$ (€/unit)	1.370	1.340	1.350	1.310	1.360	1.320	1.330	1.300
$CSS_{p1,p2}$ (€/unit)	50	35	40	20	45	25	30	15

Table 3: Substitution, refrigeration and fuel costs, and maximum load of vehicles, for pools of PLTs with PR.

p1 = PLTs	
$CBSubsDN_{p1}$	600 €
$CBSubs_{p1}$	500 €
$CRefriBCDN_{p1}$	1 €/unit/day
$CRefri_{p1}$	1,5 €/unit/day
$CRefri_u$	2 €/unit/day
$CFuel_e$	0,08 €/km
$CFuel_f$	0,14 €/km
$MaxL$	800 units

Table 4: DNs' driving distances and times from the CSTL and their maximum ages for pools of PLTs with PR.

DNs		$Dist_d$	T_d	$MaxAge_{d,p1=PLTs}$
A	Hospital de S. José	6,4 km	25 min	5 days
B	Hospital de Sta. Maria	3 km	10 min	7 days
C	Hospital de S. Francisco Xavier	12 km	20 min	3 days
D	Hospital Prof. Dr. Fernando Fonseca, EPE	11,3 km	15 min	4 days
E	Instituto Português de Oncologia de Lisboa, EPE	5,3 km	15 min	2 days

6.2. Results

The planning horizon considered was 30 days (the entire month of December of 2019). Additionally, the model is tested without considering the redistribution and returning of blood products. This way, the supplied units of pools of PLTs with PR are distributed from the BC to the DNs when needed, and any unused units at the DNs end up being wasted after reaching the respective maximum age. This modified model, with no redistribution and no returns of blood products from the DNs, is assumed to be the close-to-reality model. This way, by comparing the results of the original model (with redistributions and returns) with the latter, conclusions can be made on the benefits of this dissertation's innovative formulated model.

- **Total costs**

The total costs showed that that model 1 is more expensive than model 2. However, it is only significantly costlier for the refrigeration costs, as model 2 presents higher costs of wastage, substitution and safety stocks and the remaining costs are the same for the two models.

That said, it is possible to infer that with model 2 there is more waste of blood, more blood type substitutions, and the DN's inventory falls below the minimum level more often. For model 1, it is clear that more units are kept in storage and transported.

- **Wastage levels**

Model 2 presents higher costs of wastage, suggesting that there is more wastage for model 2 and that model 1 contributes to preventing it. In fact, although in modest quantities, the results show exactly that. In total, model 1 prevents the waste of 9 units of blood: for model 1 the total wastage is of 741 units whereas for model 2 is of 750 units.

Regarding the DNs, there is a clear minimization of waste for model 1, as it was expected since units are continuously returned to the BC after reaching their maximum age, except for DN B (*Sta. Maria*) whose maximum age is the same as the PLTs' SL (7 days). As for the BC, wastage is greater for model 1, since the returning of units

from the DNs does not necessarily mean that these will be redistributed and, if not, they end up being wasted at the BC. In case of higher demands from the DNs, the chance of redistribution could be higher, lowering the wastage at the BC. For the DNs, with the first model only 53 units are wasted, all from DN B (Sta. Maria), and with the second model 441 units are wasted (from all DNs), a much higher waste as expected. Contrarily, for the BC, model 1 results in the waste of 688 units, whereas with the second model 309 units are wasted.

- **Returns from the DNs to the BC**

As previously mentioned, with model 1, all DNs except DN B (*Sta. Maria*) can return blood units to BC, since their maximum ages are younger than the SL of the blood product. Thus, DN E (*IPO*), being the one with the lowest maximum age (of 2 days), is the DN which returned the most units to the BC.

The number of returned units influences fuel and refrigeration costs. The first are higher for model 1, so it is inferred that with model 1 there are more units in storage at the BC or at the DNs and/or that more units are transported between the two facilities. As for the fuel costs, although there are clear differences in the loads of the vehicles when returning from the DNs to the BC, since the maximum load of the vehicles considered for this model was of 800 units, the load rates at each time period are very small and so the differences between them become insignificant. Thus, fuel costs, which are calculated according to the load rates, are the same for the two models.

- **Substitution levels**

Both models need to perform blood type substitutions to meet demand and avoid shortage and model 2 is costlier than model 1 for substitution costs. The results are in line with the costs, as model 2 has a greater need for blood type substitutions, particularly 15 for transfusions at the DNs and 11 for distributions from the BC to the DNs, whereas model 1 performs less blood type substitutions, particularly 11 for transfusions and 7 for (re)distributions. Hence, with model 1 there is a better quality of service and a more efficient use of blood units when it comes to the lessen of the number of blood type substitutions, since it is considered good hospital practice to perform as many transfusions within the same blood type as possible [29].

- **Shortage levels**

For both models, there are 9 units in shortage at the 3rd day of the month, at DN E (IPO). However, these shortage levels are influenced by how the ordered quantities by the DNs are calculated. In this model, the ordered quantities are calculated depending on the previous demanded quantities. Hence, for instance, if there is short demand at a time period but a much greater demand at the next time period, then the ordered quantities would not be enough to meet the demand. This is exactly what happens at DN E, which has no demand until the third day, when its inventory is empty. So, the resulting shortage levels from these experiments are the result of this model's limitation. The utilization of, for example, forecasting methods based on the demand from the last days or months, could result in better shortage outcomes.

- **Daily inventory levels**

The results reveal that, in fact, at the DNs the inventory levels are very similar, but, at the BC, with model 1 there is a greater amount of units kept in storage. This complies with the costs and the expected, once that for model 2 the BC's inventory only depends on the monthly supply and on the units distributed to the DNs, while for model 1 it also depends on the returned units from the DNs. Thus, the results also shows that the BC's inventory for model 1 has more non-fresh units than for model 2. In fact, the average age of units (rounded) in inventory for model 1 is 4 days, whereas for model 2 is 3 days.

- **Age of transfused and (re)distributed units**

Lastly, concerning the age of the transfused, the restriction of transfusions to each DN's maximum age clearly results in a better quality service by the DNs, as the blood transfusions occur, in average, with fresher units. In case of no restrictions on the maximum age of transfusions, the average age of transfusions is higher, as it was confirmed when testing model 2 with all DNs having a maximum age of 7 days, the PLTs' SL, which resulted in an average age of transfusions of 5 or 6 days. Also as expected, for model 1 the average ages are the same or higher than for model 2, due to the possible blood reutilization.

6.3. Sensitivity analysis

Figure 7 shows how the models dealt with the total units of the month (initial DNs' inventory plus total supply of the month plus shortage units): wasted units (BC and DNs), transfused units, shortage units and units kept in inventory at the last day (BC and DNs).

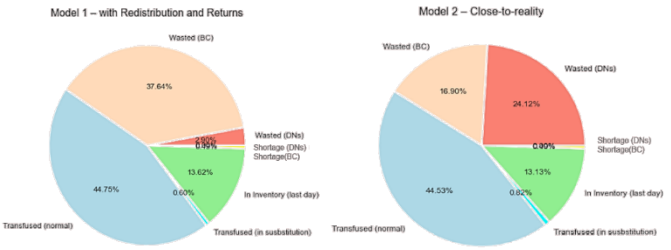

Fig. 7: Results on wastage, transfusion, shortage and remaining inventory (SL=7 days).

Overall, there is a very small difference of 0,5% between the total wastage levels of the two models tested. Yet, the goal was to minimize wastage, even if only for 9 units, was accomplished. Blood is essential and any waste should be prevented. However, the observed small difference in wastage between the two models can be influenced by other factors, such as the short SL of the considered blood product, which is the lowest SL of the other possible blood products [9]. The shorter the SL, the less time to manage and reuse units in inventory. Hence, a sensitivity analysis was performed for a scenario with a hypothetical higher SL of PLTs, of 15 days, where the maximum ages for all DNs remain the same as before, except for DN B (*Sta. Maria*) whose maximum age is the new SL.

Figure 8 shows how model 1 and model 2 dealt with the total units of the month, for a SL of 15 days, where one can clearly see the lowest waste compared to the models for a 7-day SL. As for model 1 22,54% of total units were wasted, whereas for model 2 25,0.% of total units were wasted. Hence, model 1 for a SL of 15 days minimizes the waste of units in 2,48%, a higher percentage than for a SL of 7 days (0,5%).

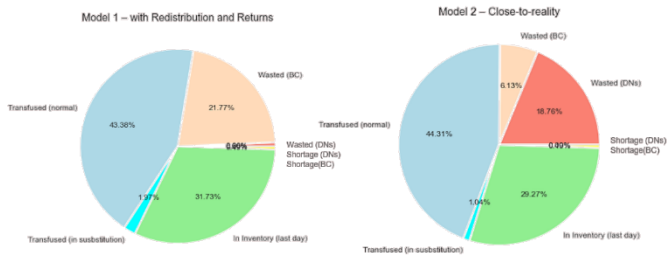

Fig. 8: Results on wastage, transfusion, shortage and remaining inventory (SL=15 days).

The results show that there is a big difference between the wastage levels for the two SLs tested, for the models with a SL of 15 days waste much less blood, precisely less 331 units for model 1 and less 295 for model 2. Overall, with a SL of 7 days, model 1 prevented the waste of 9 units, when compared to model 2. In the case of a SL of 15 days, model 1 prevents the waste of 45 units, when compared to model 2. Therefore, it can be concluded that the SL influences the wastage levels, in such way that a blood product with a higher SL and the appropriate maximum ages for the respective DNs can benefit from the redistribution and returning of units by minimizing waste. As for the ages of transfused units, it is also clear that for DN B (*Sta. Maria*) the average age is higher, as it was expected since the maximum age of this DN is the same as the SL of the product. Concerning the average age of units in inventory at the BC, the results are also as expected, with a higher average age for a SL of 15 days. Concerning

the substitution levels for (re)distribution, model 2 continues to present a higher necessity to perform blood type substitutions to meet the DNs' demands. Contrarily, for transfusions, it is model 1 the one that performs more blood type substitutions. However, overall, model 2 performs more substitutions. Yet, even if more substitutions are performed, model 1 is still beneficial in terms of wastage.

7. Conclusions and future research

The BSC is very complex due to the specificities of the blood products, such as their perishability, uniqueness or uncertain supply and demand. Thus, the importance of blood and the challenges faced by the BSC management highlight the importance of optimal and beneficial BSC management. For the Portuguese case, there are some inefficiencies that compromise the optimal functioning of the BSC, such as imbalances between supply and demand and high levels of wastage.

Thus, the objective of this work was to find the extent to which innovative approaches, based on other perishable products, can be applied to the management of the BSC and how such approaches can be tailored to fit its specific characteristics. Hence, the BSC and the AFSC were analyzed and compared, concluding that the two SCs present similarities, namely the perishability of products, safety and quality requirements and the stochastic nature of supply and demand, which means that the SCs face similar decisions, challenges and objectives. Thus, modelling insights from the AFSC were applied to the BSC, and an innovative model was formulated, focusing on the inventory management at the DNs and on the redistribution and returning of blood units from the DNs to the BC after reaching the maximum age for transfusion of the DNs. The model was applied to the Portuguese case, particularly for 5 DNs of the LVT region, and for pools of PLTs with PR (7-days SL). The goal was to minimize wastage, as well as the total costs, substitutions, shortage and the average ages of the transfused blood units. As desired, the restriction of transfusions to a maximum age resulted in a better quality service by the hospitals, as fresher units, with ages much younger than the SL, were used for transfusions. Also, with redistribution there was wastage minimization, even if in modest quantities. Additionally, a sensitivity analyses focused on the SL of the managed blood product led to the conclusion that the consideration of blood products with a higher SL might benefit even more from redistribution, by enabling units to be kept in inventory at the BC for a longer time until being redistributed.

To conclude, in this work, the model was tested with data that, while officially provided by the IPST, was assumed to be adequate to the problem and to the way the model was formulated. Hence, as a proposal for future work, besides further developing the model (with the incorporation of, for example, more details on inventory management at the BC, on collection and production and on the transportation of units between the BC and the DNs), it is suggested to complement the computational experiments using less assumed and more realistic data. Additional suggestion include: using forecasting methods for the supply at the BC and for the demand at the DNs or adding uncertainty at both levels; expanding to the different blood products and even to multiple products at the same time; expanding to more hospitals or even to the various IPST operating regions; and considering maximum transfusion ages possibly suggested by the hospitals themselves or supported by eventual studies demonstrating which age is appropriate for each treatment and patient and, consequently, each hospital. This way, it would be possible to realize whether in real dimensions such innovations, from the AFSC literature review, are beneficial to considerably reduce waste.

8. References

[1] Beliën, J., & Forcé, H. (2012). Supply chain management of blood products: A literature review. *European Journal of Operational Research*, *217*(1), 1–16. https://doi.org/10.1016/j.ejor.2011.05.026

[2] Osorio, A. F., Brailsford, S. C., & Smith, H. K. (2015). A structured review of quantitative models in the blood supply chain: A taxonomic framework for decision-making. *International Journal of Production Research*, *53*(24), 7191–7212. https://doi.org/10.1080/00207543.2015.1005766

[3] Barbosa-Póvoa, A. P. (2014). Process supply chains management - where are we? Where to go next? *Frontiers in Energy Research*, *2*(JUN). https://doi.org/10.3389/fenrg.2014.00023

[4] Escoval, M. A., & Marques, V. (2020). *Plano de Atividades 2020*. Retrieved from: https://www.ipst.pt/files/IPST/INTRUMENTOS_GESTAO/Plano_Actividades/Plano_de_AtividadesIPST_2020_Homologado.pdf

[5] Escoval, M.A., Condeço, J., Sousa, A. P., Ramoa, A., Caeiro, C., Vasconcelos, E., Miranda, I., Gonçalves, J. D., Chin, M., & Santos, M. (2021). *Relatório de Atividade Transfusional e Sistema Português de Hemovigilância 2020.* Retrieved from: http://www.hemovigilancia.net/files/RA_2020.pdf

[6] American Red Cross. (2020). *Facts About Blood and Blood Types*. Retrieved from: https://www.redcrossblood.org/donate-blood/blood-types.html

[7] American Society of Hematology (ASH). (2009). *Blood Basics*. Retrieved from: https://www.hematology.org/education/patients/blood-basics

[8] Najafi, M., Ahmadi, A., & Zolfagharinia, H. (2017). Blood inventory management in hospitals: Considering supply and demand uncertainty and blood transshipment possibility. *Operations Research for Health Care*, *15*, 43-56. https://doi.org/10.1016/j.orhc.2017.08.006

[9] Pirabán, A., Guerrero, W. J., & Labadie, N. (2019). Survey on blood supply chain management: Models and methods. *Computers and Operations Research*, *112*, 104756. https://doi.org/10.1016/j.cor.2019.07.014

[10] Meneses, M., Santos, D., & Barbosa-Póvoa, A. (2022). *Modelling the Blood Supply Chain – From Strategic to Tactical Decisions: A Review*. Instituto Superior Técnico, University of Lisbon.

[11] Nagurney, A., Masoumi, A. H., & Yu, M. (2012). Supply chain network operations management of a blood banking system with cost and risk minimization. *Computational Management Science*, *9*(2), 205–231. https://doi.org/10.1007/s10287-011-0133-z

[12] Osorio, A. F., Brailsford, S. C., & Smith, H. K. (2018). Whole blood or apheresis donations? A multi-objective stochastic optimization approach. *European Journal of Operational Research*, *266*(1), 193-204. https://doi.org/10.1016/j.ejor.2017.09.005

[13] Optimal Blood Use Project. (2010). Manual para Uso Ótimo do Sangue. *Optimal Blood Use Project*, 1–62. Retrieved from: http://ipst.pt/files/IPST/INFORMACAO_DOCUMENTACAO/manual_para_uso_optimo_do_sangue.pdf

[14] Klein, H. G., & Bryant, B. J. (2009). Pathogen-reduction methods: advantages and limits. *ISBT Science Series*, *4*(1), 154–160. https://doi.org/10.1111/j.1751-2824.2009.01224.x

[15] Araújo, A. M. (2018). *Blood Supply Chain Planning : the case of the Southern region of Portugal* (Issue October). [Master's thesis, Instituto Superior Técnico, University of Lisbon].

[16] Osorio, A. F., Brailsford, S. C., Smith, H. K., Forero-Matiz, S. P., & Camacho-Rodríguez, B. A. (2017). Simulation-optimization model for production planning in the blood supply chain. *Health Care Management Science*, *20*(4), 548–564. https://doi.org/10.1007/s10729-016-9370-6

[17] Duan, Q., & Liao, T. W. (2014). Optimization of blood supply chain with shortened shelf lives and ABO compatibility. *International Journal of Production Economics*, *153*, 113–129. https://doi.org/10.1016/j.ijpe.2014.02.012

[18] Francisco, S. P. (2021). *Optimal configuration and planning of a blood supply chain network under an uncertain environment* (Issue November). [Master's thesis, Instituto Superior Técnico, University of Lisbon].

[19] Sousa, J. P. A., & Sousa, G. de. (2017). *Plano estratégico 2017-2019*. Retrieved from: http://www.ipst.pt/files/IPST/INTRUMENTOS_GESTAO/Plano_Estrategico_2017_2019_IPST_homologado.pdf

[20] Torrado, A. S., & Barbosa-Póvoa, A. (2022). Towards an Optimized and Sustainable Blood Supply Chain Network under Uncertainty: A Literature Review. *Cleaner Logistics and Supply Chain*, 100028. https://doi.org/10.1016/j.clscn.2022.100028

[21] Amorim, P., Meyr, H., Almeder, C., & Almada-Lobo, B. (2013). Managing perishability in production-distribution planning: a discussion and review. *Flexible Services and Manufacturing Journal*, *25*(3), 389-413. https://doi.org/10.1007/s10696-011-9122-3

[22] Mirabelli, G., & Solina, V. (2022). Optimization strategies for the integrated management of perishable supply chains: A literature review. *Journal of Industrial Engineering and Management*, *15*(1), 58-91. http://dx.doi.org/10.3926/jiem.3603

[23] Yadav, V. S., Singh, A. R., Gunasekaran, A., Raut, R. D., & Narkhede, B. E. (2022). A systematic literature review of the agro-food supply chain: Challenges, network design, and performance measurement perspectives. *Sustainable Production and Consumption*, *29*, 685-704. https://doi.org/10.1016/j.spc.2021.11.019

[24] Tsolakis, N. K., Keramydas, C. A., Toka, A. K., Aidonis, D. A., & Iakovou, E. T. (2014). Agrifood supply chain management: A comprehensive hierarchical decision-making framework and a critical taxonomy. *Biosystems engineering*, *120*, 47-64. https://doi.org/10.1016/j.biosystemseng.2013.10.014

[25] Esteso, A., Alemany, M. M., & Ortiz, A. (2018). Conceptual framework for designing agri-food supply chains under uncertainty by mathematical programming models. *International Journal of Production Research*, *56*(13), 4418-4446. https://doi.org/10.1080/00207543.2018.1447706

[26] Farahani, R. Z., Rezapour, S., Drezner, T., & Fallah, S. (2014). Competitive supply chain network design: An overview of classifications, models, solution techniques and applications. *Omega*, *45*, 92-118. https://doi.org/10.1016/j.omega.2013.08.006

[27] Singh, A. K., Subramanian, N., Pawar, K. S., & Bai, R. (2018). Cold chain configuration design: location-allocation decision-making using coordination, value deterioration, and big data approximation. *Annals of Operations Research*, *270*(1), 433-457. https://doi.org/10.1007/s10479-016-2332-z

[28] Qi, C., & Hu, L. (2020). Optimization of vehicle routing problem for emergency cold chain logistics based on minimum loss. *Physical Communication*, *40*, 101085. https://doi.org/10.1016/j.phycom.2020.101085

[29] Meneses, M. (2019). *Otimização do fluxo da cadeia de abastecimento do sangue - Gestão de inventário em bancos de sangue hospitalares.* [Master's thesis, Instituto Superior Técnico, University of Lisbon]