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Innovative approaches to optimal blood supply chain management problems

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Preface

The work presented in this thesis was performed at Instituto Superior Técnico (Lisbon, Portugal), during the period January-October 2022, under the supervision of Prof. Daniel Rebelo dos Santos and Prof. Ana Paula Ferreira Dias Barbosa Póvoa.

Declaration

I declare that this document is an original work of my own authorship and that it fulfills all the requirements of the Code of Conduct and Good Practices of the Universidade de Lisboa.

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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

Resumo

O sangue é fundamental na vida, desempenhando um papel essencial em várias necessidades humanas básicas. Contudo, é perecível, único, e a sua oferta e procura são incertas, pois a oferta depende de doações voluntárias não remuneradas e o futuro é imprevisível. A importância do sangue, perecibilidade, singularidade e incerteza aumentam a complexidade da gestão da sua cadeia de abastecimento. De facto, o caso português apresenta ineficiências, particularmente elevados níveis de desperdício, para plaquetas. Logo, é de grande importância haver um método eficiente e sustentável, capaz de resolver as ineficiências existentes. Assim, foi realizada uma revisão literária sobre a cadeia de abastecimento do sangue e outras cadeias de abastecimento perecíveis, nomeadamente a cadeia agro-alimentar, para encontrar possíveis transferências de conhecimento da cadeia agro-alimentar para a do sangue. Daí, foi desenvolvido um modelo inovador, principalmente focado na minimização do desperdício e no aumento da qualidade das transfusões, que introduz uma idade máxima, específica para cada hospital, correspondente à idade máxima para transfusões e para além da qual os hospitais devolvem o sangue ao centro de sangue, para ser redistribuído a outros hospitais. O modelo foi aplicado ao caso português, para pools de plaquetas com redução patogénica, e os resultados mostraram que, embora em quantidades modestas, a redistribuição de sangue é benéfica para reduzir o desperdício. A idade média das transfusões e o número de substituições também apresentaram melhores resultados. Análises adicionais obtiveram uma maior redução do desperdício ao considerar uma vida útil maior.

Keywords:

Sangue, Cadeia de Abastecimento do Sangue, Cadeia de Abastecimento Agro-Alimentar, Produtos Perecíveis, Otimização, Desperdício

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List of Abbreviations

AFSC – Agro-Food Supply Chain

ASH – American Society of Hematology

BC – Blood Center

BSC – Blood Supply Chain

CCP – Chance Constraint Programming

CRS – Centros Regionais de Sangue

CS – Collection Site

CSR – Corporate Social Responsability

CSTC – Centro de Sangue e da Transplantação de Coimbra

CSTL – Centro de Sangue e da Transplantação de Lisboa

CSTP – Centro de Sangue e da Transplantação do Porto

CSTs – Centros de Sangue e da Transplantação

DES – Discrete Event Simulation

DN – Demand Node

EPE – Entidades Públicas Empresariais

ESL – Expected Shelf Life

EWA – Estimated Withdrawal and Aging

FEFO – First-Expired-First-Out

FIFO – First-In-First-Out

FMP – Fuzzy Mathematical Programming

HBV – Hepatitis B Virus

HCV – Hepatitis C Virus

HIV – Human Immunodeficiency Virus

HTLV – Human T-Lymphotropic Virus

ICT – Information and Communication Technologies

INS – Instituto Nacional de Sangue

IPO – Instituto Português de Oncologia

IPS – Instituto Português do Sangue

IPST – Instituto Português do Sangue e da Transplantação, IP

KPI – Key Performance Indicator

LIFO – Last-In-First-Out

LVT – Lisboa e Vale do Tejo

MILP – Mixed-Integer Linear Programming

MINLP – Mixed-Integer Non-Linear Programming

OIR – Old Inventory Ratio

PLTs – Platelets

PR – Pathogenic Reduction

RBCs – Red Blood Cells

RO – Robust Optimization

SC – Supply Chain

SDR – Service Distance Requirement

SDS – System Dynamics Simulation

SL – Shelf Life

SP – Stochastic Programming

TSSP – Two-Stage Stochastic Programming

WB – Whole Blood

1. Introduction

The introduction chapter aims to introduce the problem addressed in this dissertation, starting, in section 1.1., by contextualizing blood and presenting the motivations for this work. Then, at sections 1.2. and 1.3., the objectives and the structure of the dissertation are presented, respectively.

1.1. Contextualization and motivations

Blood is very important to life, playing a necessary role in basic human needs such as breathing, nutrition, regulation and protection of the human body. It's of vital nature, with many different functions, including the transport of oxygen and nutrients to the organs and tissues, the formation of blood clots to prevent excess blood loss, the carrying of cells and antibodies to infections sites, the transport of waste products to the kidneys and liver in order for the blood to be filtered and cleaned, and the regulation of the body's temperature (ASH, 2009).

In fact, in ancient times, humans have observed that the loss of blood could lead to death. However, only at 1628 did William Harvey recognized the mechanism of blood in the human body: blood is pumped by the heart through arteries and returns back through veins. Since then, experiments with transfusions, i.e., operations in which blood or blood components (Whole Blood (WB), Red Blood Cells (RBCs), Platelets (PLTs), Plasma or Cryo) are transferred from one organism, the donor, into the bloodstream of another, the recipient, were performed, but not always successful. In the 19th century, James Blundell, a British obstetrician, performed the first ever recorded successful transfusion on a mother suffering from post-partum hemorrhage, using blood from her husband. In his following transfusions, two problems kept emerged: the blood frequently clotted during the procedures, and about half of the patients suffered from severe reactions, leading some of them to death. The first problem occurred since no anticoagulants, i.e., solutions that prevent or reduce blood from clotting, were used in the procedures, for only in the 20th century did anticoagulant solutions were introduced. The second problem derived, of course, from the, at the time, unknown blood types and compatibilities. Only in the 20th century did Karl Landsteiner and his students discovered the A, B, AB and O blood types, today designated as the ABO blood group system. This discovery dramatically reduced the number of deaths from transfusion procedures. However, some remaining reactions, such as fever, were still observed, caused by another, at the time, unknown blood group system, which was only discovered in 1939 by Philip Levine and R.E. Stetson – the Rhesus system (Government of Malta, 2022).

Blood is not an ordinary commodity, having an outstanding impact in human lives. 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 (Beliën & Forcé (2012) and Osorio et al. (2015)). Hence, optimizing the BSC processes is of vital importance.

The Blood Supply Chain (BSC) is constituted by blood facilities, which include Collection Sites (CSs), Blood Centers (BCs) and Demand Nodes (DNs) (such as hospitals or clinics), that ensure its functioning and the safety and quality of the blood, throughout its four main stages: collection, responsible for obtaining the necessary blood products from donations; production, where the collected blood products are tested and separated into its components; storage, where blood is kept in inventory and managed before being distributed; and distribution, to demand points for transfusions (Barbosa-Póvoa, 2014). 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. Hence the importance of BSC management.

Supply Chains (SCs) are of great importance because, as stated by Barbosa-Póvoa (2014), they are "the organizations systems responsible for delivering the products in the right location with the right quantity and at the right time". Because these organizations systems usually involve a great number of entities, materials and information, the SC management becomes a challenging and complex process. According to Meneses et al. (2022), SC management is defined as the integration of the network facilities and stakeholders for coordinating information, material, and financial flows in order to efficiently fulfil customer demands and improve the competitiveness of a SC as a whole. Besides, in order to meet its goals, SC management must consider several parameters, such as costs, distances, sustainability and the particularities of the managed products.

Blood products are perishable, i.e., blood has a limited Shelf Life (SL) after which it must be discharged. Also, blood products requires high service levels, such as specific storage and transport conditions, quality and product disposal, 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, meaning that the blood supply is uncertain over time, along with demand, which is also uncertain, being both supply and demand two important parameters of stochastic nature. Since blood products are vital, they should always be available when needed, but their wastage should always be avoided. Because of these previous factors, BSC management is highly complex, often facing issues of planning, coordination and cooperation, in its multi-facility and multi-product network.

In the specific case of Portugal, where donations come from voluntary and unpaid donors, there is, amongst other tendencies and diseases, a trend towards an ageing population, meaning that health care will become increasingly important and necessary for the Portuguese population, which, consequently, will imply a greater demand for blood products (INE, 2020). Therefore, it is increasingly important to have an efficient, sustainable and effective BSC management, ensuring that the entire population will have access to blood products in DNs, even given the uncertainty of supply and demand, keeping the healthcare service levels and the patients' safety.

Thus, given the importance of blood products and the main challenges faced by the BSC management, this topic is research-worthy and deserves all the attention.

1.2. Objectives of the dissertation

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, such as the uncertainty in supply, uncertainty in demand and the perishability of the blood products. 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.

Following this, the development of this dissertation is carried out in accordance with the following methodology, as it is illustrated in figure 1:

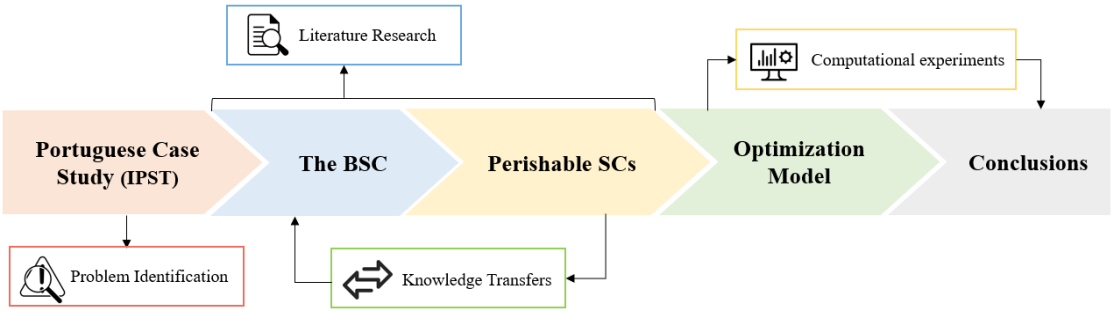

Figure 1 – Methodology.

1) The presentation of the organization and functioning of the BSC in Portugal through a case study on *Instituto Português do Sangue e da Transplantação*, IP, identifying its functioning, main stages, performances and main inefficiencies.
2) A literature review and classification of the BSC management, analysis on the problems characteristics from each stage of the BSC, important parameters to measure its performances and methods;
3) The positioning of the BSC management problem in the SC management review/classification by stating the differences and the similarities between the networks;
4) A literature review and classification of SC management problems for other perishable products, in particular agri-foods, including analysis on the problems characteristics and methods;
5) The discussion of possible knowledge transfers from the problems, characteristics and methods identified in the Agro-Food Supply Chain (AFSC) management reviews to the BSC management;
6) The development and implementation of an optimization model and a solution approach based on the main findings of 5;
7) Computational experiments, leaning on the Portuguese case study and using data from *Instituto Português do Sangue e da Transplantação*, IP;
8) Recommendations and managerial insights for BSC management.

1.3. Structure of the dissertation

To facilitate the reading of this dissertation, it's important to outline its structure and to resume the content from each chapter. All chapters start with a brief introduction to introduce the topics, and end with a small conclusion on those same topics. Therefore, this dissertation is structured into four chapters, organized as follows:

- **Chapter 1 – Introduction.**

This chapter introduces the problem, contextualizing blood and presenting the motivations for this work, explaining some of the main characteristics of the BSC and the main factors that increase its complexity, and, at the end, presenting the objectives and structure of the dissertation.

- **Chapter 2 – Case study: Instituto Português do Sangue e da Transplantação, IP**

This chapter points out the Portuguese BSC and its management, along with its functioning and main problems and inefficiencies, by presenting *Instituto do Sangue e da Transplantação*, IP, which is responsible for the regulation and functioning of the BSC activity in Portugal. From this chapter, the main problems on the topic are identified.

- **Chapter 3 – Blood supply chain and blood supply chain management.**

This chapter presents a literature review on the BSC. Firstly, some concepts of SCs and SC management are explained, and the main characteristics of the blood products are exposed. Then, the BSC is reviewed, its network, main stages, main characteristics, and the main gaps found from literature, along with the main methodologies to optimize the BSC are enumerated. At the end, the main problems and subsequent decisions, constraints, sources of uncertainty and main objectives for modelling the BSC are presented.

- **Chapter 4 – Perishable supply chains and perishable supply chain management**

In this chapter, examples of other SCs for perishable products are presented from literature review along with their unique features. Particularly, the AFSC is detailed, describing its main characteristics, stages, management decisions, problems, constraints, uncertainties and objectives. At the end, innovative approaches from AFSC management are explored, in order to find possible transfers of knowledge from the AFSC to the BSC.

- **Chapter 5 – Problem definition and model formulation**

This chapter describes the problem addressed in this work and formulates the proposed BSC innovative model for inventory management and (re)distribution, based on the review made for the AFSC. All the sets, parameters, variables, constraints, calculations and the objective function are detailed in this chapter.

- **Chapter 6 – Results and discussion**

In this chapter, the results from the computational experiments of the optimization model previously implemented in chapter 5 are detailed and discussed, along with the main findings from this research.

- **Chapter 7 – Conclusions and future work**

This is the final chapter of the dissertation, which presents the relevant conclusions from the presented work, along with insights for future research on this topic.

2. Case study: Instituto Português do Sangue e da Transplantação, IP

This chapter presents a case study for the Portuguese BSC, referring to *Instituto Português do Sangue e da Transplantação* (IPST), the entity responsible for the regulation and management of all blood-related activities in Portugal. Firstly, section 2.1. historically contextualizes IPST and section 2.2. presents how it is structured and organized. Then, section 2.3. describes the Portuguese BSC and each of its main steps – collection, processing and testing, inventory, and distribution – in subsections 2.3.1, 2.3.2, 2.3.3 and 2.3.4, respectively. Section 2.4. analyses the Portuguese BSC performance for both collection and transfusion, in subsections 2.4.1 and 2.4.2, respectively. Finally, section 2.5. points out the main problems and inefficiencies faced by the blood scene in Portugal. At the end, section 2.6. makes conclusions on this chapter.

2.1. Historical contextualization

In Portugal, the generalization of the blood transfusion practice only started to happen in the last half of the 20th century. In January of 1958, the first organic structure responsible for transfusion medicine was created and designated as *Instituto Nacional de Sangue* (INS), but a clear strategic policy was not achieved and effective coordination did not take place. In 1976, from work developed by a group of recognized professionals, and after hearing the concerned institutions on the creation of a national blood service, it was outlined the design for a future national blood transfusion network. In the 1980s, a raising demand for blood and its high commercial prices, due to the insufficient quantity of blood and the emerging of new dangerous and contagious diseases, raised the attention for the absence of a clear and efficient national organization. It was also then that medical, therapeutic and technological advances increased greatly, allowing further generalization and improvement of transfusion therapy. However, these development of the structure of the healthcare delivery, along with the sophistication of medical and surgical techniques, led to growing needs for blood components and to the unplanned spread of multiple blood establishments, increasing the complexity of the network's logistics. Consequently, it was so determined the need for a system to precisely define rules for the transfusion process in Portugal. INS was then exposed by its fragilities in these matters, and, in September of 1990, it was restructured into *Instituto Português do Sangue* (IPS), with defined attributions and specific competences. IPS appeared as a public organism, provided with legal personality and technical, administrative and financial autonomy, and integrated the network of personalized services of the Ministry of Health. The purpose of the national blood service was to coordinate and regulate the BSC and its facilities, by making use of an integrated network of services with the appropriate technical, human and material resources to the functions assigned to them: IPS was responsible for the sector's normative and coordination competencies; the Regional BCs (*Centros Regionais de Sangue* – CRSs) were responsible for the operational competencies of collection, processing, distribution and regional technical supervision; and the Hospital Immunohemotherapy Services were responsible for, besides the collection and production processes in healthcare facilities, the practice of a global quality transfusion. In 2007, it was established a new organic structure for the IPS, IP, with the goal to regulate, at national level, the activity of transfusion medicine and ensure the availability and accessibility of quality, safe and effective blood components (IPST, 2020a).

Later, in February of 2012, the system was again restructured, with IPS incorporating the functions of the Histocompatibility Centers and also part of the Blood and Transplantation Services Authority, which became extinct

by the merger. All the competencies previously attributed to these entities came under the responsibility of the new and actual system, designated by its present name (IPST, 2020b).

The actual IPST is, so, a public institute that operates under attributions from the Portuguese Ministry of Health, and consequently, under the superintendence and tutelage of the Secretary of State for Health. It runs with technical, administrative and financial autonomy, it has its own assets, and it is a central body, with its headquarters in the city of Lisbon, the Portuguese capital, having jurisdiction over the entire country's territory (IPST, 2020b). Its adopted values result from the IPST's position as an institution dedicated to the support of human life through the areas of blood and transplantation, and, consequently, its mission is to ensure and regulate, at national level, the activity of transfusion medicine and transplantation, and ensure the donation, collection, testing, processing, preservation, storage and distribution of human blood, blood components, organs tissues and cells of human origin (IPST, 2020c).

2.2. Organizational structure

Relatively to its internal structure, IPST is organized into 3 major constituent entities: the Board of Directors, the Fiscal Council, and the Consultant Board for Blood, Histocompatibility and Transplantation. The first is structured into national organizational divisions and territorially decentralized services, which are the three former CRSs, that in 2012 were renamed as *Centros de Sangue e da Transplantação* (CSTs) (Escoval & Marques, 2020a).

The 3 CSTs, although geographically located in distinct areas of Portugal, together 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, as it is illustrated in figure 2. Although the CSTs are decentralized services from IPST, they still have hierarchical dependence and the same attributions as IPST, at the level of each respective geographical region. This means that the Technical Directors of each CST determine and propose activities and necessities to the Board of Directors, such as the acquisition of material resources and equipment, the hiring of human resources and other infrastructure needs. Besides, IPST then divides into two functional areas, the Functional Area of Blood (the area to discuss in this work), and the Functional Area of Transplantation.

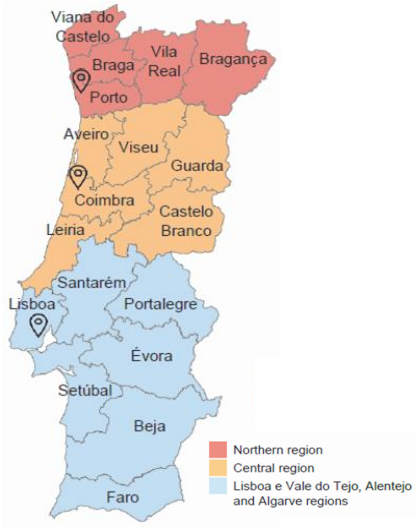

Figure 2 – Regions of operation of the CSTs. Source: Francisco (2021).

2.3. The Portuguese blood supply chain

The Portuguese BSC is composed by 3 CSTs, as mentioned in section 2.2., and 24 hospital blood units, distributed along Portugal's mainland in the regions covered by the CSTs, which means that, as mentioned later in this work in section 3.4., the Portuguese BSC network is configurated as a centralized system. The hospital blood units are the facilities qualified to collect the donations of blood, that in Portugal depend on voluntary, unpaid and anonymous donors. The CTSs are responsible for the processes of collection, processing, storage and distribution of the blood products and its flow articulation with DN, in each respective region (Escoval et al., 2021).

The Functional Area of Blood, which is the party where IPST operates with all blood-related activities, englobes 4 main processes – collection, production, storage and distribution. Besides the processing of blood into its components, the production process also englobes several laboratory tests, such as for immunohematology, transmissible agents, platelet immunology and cryobiology, which are not all performed by the three CSTs. As for the production of blood components, it is only performed in the CSTL and the CSTC. However, all three CSTs perform collection (by WB or apheresis), storage and distribution of blood components.

2.3.1. Collection

For the Portuguese BSC, there are 2 possible methods for collecting blood: WB or apheresis. The most common is the WB donation, which consists of extracting about 450ml of blood using collection bags, to then be subjected to the fractionation process to obtain the different blood components – RBCs, PLTs, Plasma and Cryoprecipitate Antihemophilic Factor (also called Cryo). Apheresis directly extracts one or more blood components and automatically returns the remaining blood to the donor. This second method is not as used, as it presents certain disadvantages, such as the longer donor time needed, the higher costs and the special conditions that donors need to meet in terms of weight and Hb levels to be able to donate RBCs, for example, by apheresis (Osorio et al., 2018).

Donations of blood in Portugal can be performed in the CSTs, in hospital blood units, in mobile venues or in bloodmobiles, by collection sessions dynamized by the CSTs. In case of the CSTs and hospital blood units, that can perform both WB and apheresis donations, donors can appear at these facilities at any time to donate blood. However, in mobile venues, usually restricted to the WB collection method, the collection sessions are organized by the CSTs together with donor associations, local authority bodies or even companies and cultural associations. When a collection session is organized, the responsible association notifies the closest CSTs, which needs to ensure that the right conditions of space, the plan and the schedule for the blood collection session are in order. Donors also need to meet some requirements in order to donate blood, such as having between 18 and 65 years old, carry a healthy lifestyle, weight over 50 kg, etc. The conditions for the facilities of collection include having a ventilated and accessible space with sanitary conditions, washable floor, several points of light, etc., and having spaced available areas for the steps performed during a collection session, represented in figure 3: the registration of donors (1), the collection (5), and the post-donation meal (6). If not in order, the CSTs can provide an adequate bloodmobile for the session, in case the parking lot to place the bloodmobile has all the requisite conditions as well (IPST, 2020d).

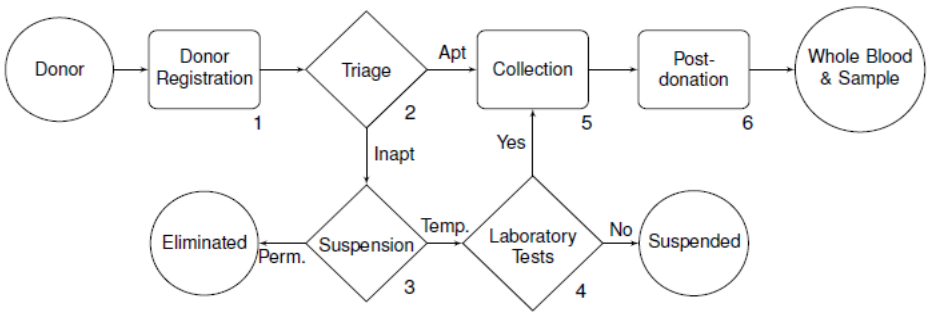

Figure 3 – Blood collection process. Source: Araújo (2018).

The blood collection process that occurs in Portugal is standardized, and complies the 6 processes illustrated in figure 3: 1) Safe identification of donors and registration; 2) Confirmation of the identification and consent of donors, suitability interview, and eligibility assessment. If eligible, a number is assigned to the donor and the related donation and all of its associated components, samples and records; 3) If inapt for collection, donors can be temporarily or permanently suspended; 4) If temporarily suspended, it is assessed if donors need to collect samples for further analysis, and, if so, a number is attributed to this donor for laboratory testing; 5) Identification of the donor, confirmation of its number in the consent form, the sampling tube and records, evaluation of the sterilization and quality of the puncture site and materials, and identification of collection bags and tubes. Right after collection, blood and blood components need to be identified and placed in controlled and validated conditions. 6) The donor is kept under vigilance in a post donation area where a light meal is provided (Rautmann et al. (2017) and Araújo (2018)). After this process, the collected blood is transported to the production facilities, to be processed and tested.

2.3.2. Processing and Testing

Production facilities are located in the CSTs and in some hospital blood units' laboratories, at which, after the collection sessions, the donations arrive for testing and processing. In Portugal, a sample of blood from each donor is taken, before collection, for laboratory testing, and the remaining collected blood is then processed.

Nowadays, in Portugal, besides testing the collected blood for the ABO and Rh blood group, blood is also tested for the human immunodeficiency virus (HIV), hepatitis B and C (HBV and HCV), the human T-lymphotropic virus (HTLV), which can trigger cancer, and *Treponema pallidum*, which causes syphilis. Other tests may also be performed according to risk factors from donors, such as, in 2020, for *Plasmodium spp*, a parasitic agent, for which its testing depends on the assessment of the donor's risk of exposure to the agent.

As for the processing, the WB collected is subjected to the separation process (fractionation), in which the bags used (commonly Top and Bottom bags) are centrifuged and then placed in a semi-automatic machine to separate the blood components according to weight. After this process, each separated blood component needs to meet specific requirements. In Portugal, the components processed in larger quantities are RBCs, then PLTs and Plasma and, in much lower quantities, Cryo (Escoval et al., 2021). Also, for all these blood products the removal of the white blood cells, or leukocytes, is mandatory (Optimal Blood Use Project, 2010). Regarding RBCs, these are stored overnight and in the morning, if the laboratory tests are favorable, the units have their labels verified and then are stored in the specific required conditions and sorted by proximity to the validity date. As for the PLTs (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 4 units of buffy coats of the same ABO blood group type 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 increases their short SL from 5 to 7 days. Finally, as for Plasma, the last most processed blood component, after the separation, Plasma units are immediately frozen for 45 minutes in an ultra-rapid chamber, and then stored in the specific required conditions. But, since Plasma can have different purposes, there are diverse treatments for Plasma units, such as inactivating it by *amotosalen*, producing quarantine Plasma or even fractionating it into albumin or factor VIII, for blood clotting (Araújo (2018) and Escoval et al. (2021)).

2.3.3. Inventory

After the blood products are processed and tested, before being shipped to the DNs they are stored according to each component's specific storage conditions. In the CSTs, blood is stored until being shipped to the DNs, and then in the hospital blood banks, in case it is required for transfusion. The short perishability of blood products is very challenging for inventory management of blood, since, if the SL is exceeded, the products are discarded, which is to prevent due to the blood's uniqueness and vital nature.

Although there's not much information available from IPST on inventory management for the Portuguese BSC, it can be assumed that the FIFO (First-In First-Out) issuing policy, further described in section 3.5.3, is the adopted one, once that, according to literature review, this is considered to be the most efficient issuing policy to prevent wastage, minimize shortages and outdated units, and average inventories. The quantity of blood kept in inventory depends on the average daily activity and demand of the DNs served by the CSTs, based on historical data, forecasts and clinical knowledge. Hence, it is also assumed that the review periodicity is of 1-day for the DNs to place orders to the CSTs, as, according to Duan & Liao (2014) and Osorio et al. (2017), it is the most common review periodicity, as it is also further described further in section 3.5.3. Crossmatching tests are also performed at this stage, to test the compatibility between patients and blood products. Although no official information was found on this matter for the Portuguese BSC, it can be assumed that hospitals and blood banks consider the existence of 2 types of inventory, *assigned* and *unassigned*, and crossmatching policies, such as the ratio between the total number of crossmatched units and transfused units, called the crossmatch-to-transfusion ratio (C/T ratio), that should be close to 1, and the crossmatch release period, that should be as short as possible, which are also further described in section 3.5.3.

2.3.4. Distribution

Official information on the distribution of blood products 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: Porto → Coimbra → Lisboa → Algarve, and vice-versa. However, 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 (J. P. A. Sousa & Sousa, 2017).

After the DN's daily requests for blood, these are registered and an on-call doctor from the CSTs allocates the units. According to Araújo (2018), the CSTL acts in accordance with the following rules for distribution: 1) CSTL

stock, so that it is never over distributed in case of emergencies; 2) Hospitals' stock, so that the on-call doctor understands if it is a pressing need; 3) Distance to the hospitals, because further located hospitals should be prioritized, since in case of need the closest hospitals are easier to supply with extra units); 4) Type of hospital, since hospitals with open ERs or maternities have priority; 5) Hospital blood units, since hospitals without blood collections have priority. Also, according to Araújo (2018), for the CSTL, the distribution of blood products to the DNs is performed by technicians from the hospital blood banks during the mornings, but along the day, emergency requests may also arrive, if approved by the on-call doctor.

2.4. The Portuguese blood supply chain in numbers

The development and implementation of the Portuguese Hemovigilance System (*Sistema Português de Hemovigilância* – SPHv), that derives from the cooperation between Institutions from the National Health Service, is a real proof of the concern and commitment of all professionals to provide the best health care to the citizens. This system, which as implemented in Portugal in 2008, is a centralized surveillance system that covers the whole transfusion chain, including the follow up of blood donors, collects information regarding unexpected or undesired effects from the collection to the transfusion of blood and blood components and takes measures to prevent the occurrence or recurrence of some of these incidents/events (IPST, 2020e).

Every year there are new notifiers and institutions included in the system. In fact, in 2018 and 2019, there were 253 and 259 registered institutions, respectively (Escoval et al., 2020). By the 31st of December of 2020, the SPHv had four more registered private institutions, so a total of 263 institutions registered: 183 were private (69,58%), 80 were public (30,42%), and 60,08% were transfusion points. The total of these 263 institutions participated for the process of recording information on blood and transfusion related activities from 2020, allowing for a more detailed and veridic analysis on this matters. The characterization of these institutions according to the activities developed is presented in table 1, which shows that, from all the 263 institutions registered, only 31 performed collection and 254 performed transfusion.

Table 1 – Number of registered institutions per activity performed, in 2020 (adapted from Escoval et al. (2021)).

Activity	Collection	Processing	Testing	Distribution	Availability	Transfusion
Yes	31	25	26	81	103	254
No	232	238	237	182	160	9

Following this, in order to understand the needs and constraints of the Portuguese BSC, and therefore its performance, data from IPST and the registered institutions in the SPHv on collection and transfusion are analyzed in sections 2.4.1 and 2.4.2, respectively, where the most relevant trends are identified.

2.4.1. Collection Performance

As illustrated in table 2, both the number of donations and donors have been decreasing over the last years, with consistently negative annual variation rates. This was, of course, even more aggravated in 2020 by the pandemic situation of COVID-19, having a great impact on blood stocks during that year.

Table 2 – Evolution of donation rates from 2011 to 2020 (adapted from Escoval et al. (2021)).

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Donors / 1000 inhabitants	27,12	24,92	23,78	22,69	22,39	21,74	21,09	20,32	20,06	18,86
Variation of donors (%)	-8,26	-8,83	-4,79	-4,80	-1,33	-2,99	-3,09	-3,80	-1,31	-6,34
Donations / 1000 inhabitants	41,09	39,13	36,18	35,35	33,76	33,40	32,41	31,41	31,03	28,80
Variation of donations (%)	-2,12	-5,01	-8,15	-2,35	-4,72	-1,07	-3,08	-3,17	-1,22	-7,76

According to J. P. A. Sousa & Sousa (2017), 35 donations per 1000 inhabitants per year, regularly distributed and according to plan and need, is what was desirable to meet Portugal's blood needs from 2017 to 2019. From the data in table 2, besides the constant reduced number of donors, it is clear that the number of donations per 1000 inhabitants was below 35 in that year gap, indicating that the blood needs were not ensured from 2017 to 2019. In 2020 the number of donations had an even bigger decrease, falling down to 28,80 donations per 1000 inhabitants that year.

From all the blood donations performed in 2020, 57,68% were collected by IPST (0,44% more than the 57,24% in 2019), and the remaining 42,32% were collected in hospitals. This proves the importance of IPST and its activities developed for the collection of blood, and the importance of having hospital-based collections.

The data on collection trends per region, in comparison with data from 2019, shows the following: the Northern region, together with CSTP, collected 42,09% of the national donations (42,79% in 2019, with precisely 11585 less donations); the Central region, together with CSTC, collected 20,37% of the national donations (21,27% in 2019, with precisely 7345 less donations); and, finally, the LVT region, together with CSTL, collected 27,08% of the national donations (25,71% in 2019, with precisely 1762 more donations) (Escoval et al., 2021).

Concerning the donations, table 3 shows the total number of homologous and autologous donations in 2020, from where it's concluded that about 98% of donations in 2020 were of WB and the remaining 2% were of donations by apheresis, with PLTs being the most collected blood components using this method. As for the production step, table 4 presents the number of components' units produced and validated in 2020. For RBCs, there's a trend observed since 2013, with a decrease in the number of RBCs produced, proportional to the decrease in the number of donations. Regarding PLTs, since 2012 there has been a slight increase of PLTs production from apheresis (in 2019, 772 less units were produced), an increase of production of PLTs pools with a progressive increase of pools with PR (9987 units, in 2019) and a decrease of production of PLTs from WB. Pathogenic reduction or inactivation (PR) is a proactive approach to reduce transfusion-transmitted infections, protecting from infectious agents and potentially impact the safety of blood transfusions (Klein & Bryant, 2009). As for the remaining, in 2020 there was constant fresh frozen Plasma production, while the production of cryoprecipitates decreased significantly (in 2019, 441 more units were produced).

Table 3 – Total number of homologous and autologous donations, in 2020 (adapted from Escoval et al. (2021)).

Total number of donations	WB	Apheresis				
		RBCs	PLTS	Plasma	Multicomponents	Granulocytes
Homologous	282.406	11	4.464	9	1.068	0
Autologous	39	0	0	0	0	0

Table 4 – Nr. of units of blood components produced and validated, in 2020 (adapted from Escoval et al. (2021)).

RBCs (WB)	PLTs (apheresis)	Pool of PLTs	Pool of PLTs (w/ PR)	PLTs (WB)	Plasma	Cryoprecipitates
276.857	5.813	15.005	21.640	15.214	209.498	55

According to Escoval & Marques (2020b) on the strategic plan for 2020-2022, one of the measures to implement is to have an appropriate collection of blood and blood components to their consumption, to prevent wastage. By using apheresis, the most desired components could be more adequately collected. In fact, this could prevent the discharge of units due to outdating, which remains in 2020 to be the most frequent cause of waste for all components, pointing out the probable difficulty of management, the relationship between supply and demand, and the issues related to the pressure to have components in stock for emergencies or unexpected situations (Escoval et al., 2021).

2.4.2. Transfusion Performance

To evaluate the performance of transfusion activities, table 5 displays the units of RBCs and PLTs transfused and patients, from 2015 to 2020. The remaining blood components, Plasma and Cryo, aren't considered for this analysis since their SLs correspond to 1 year, meaning that produced units from a certain year may only be transfused in the following year, which can also be considered a bad indicator for wastage of blood units (Francisco, 2021). Regarding RBCs, there's a trend for a decreasing number in RBC transfusions, presenting mostly negative variations in both annual transfused units and patients, except in 2019 for both and in 2016 for the patients' annual variation, which presented positive variations. As for PLTs, this trend is not totally shared, since there's more of an increasing trend for transfusion of PLTs, more precisely for PLTs collected by apheresis and in pools of PLTs. For PLTs processed from WB, there's both positive and negative variations.

Table 5 – Units of components transfused, and patients, from 2015 to 2020 (adapted from Escoval et al. (2021)).

Year		**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
RBCs	Units	312.924	306.841	300.334	290.001	293.982	272.811
	Variation (%)	-4,63	-1,94	-2,12	-3,44	+1,34	-7,17
	Patients	92.271	93.864	93.801	91.642	91.734	85.368
	Variation (%)	-6,99	+1,73	-0,07	-2,30	+0,10	-6,94
PLTs (pool and apheresis)	Units	37.159	38.012	39.867	39.047	40.252	39.417
	Variation (%)	-0,87	+2,30	+4,88	-2,06	+3,09	-2,07
	Patients	10.609	10.728	12.075	10.463	11.779	11.501
	Variation (%)	+1,45	+1,12	+12,56	-13,35	+12,58	-2,36
PLTs (WB)	Units	9.153	10.118	9.363	8.441	8.498	6.820
	Variation (%)	+2,19	+10,54	-7,46	-9,85	+0,68	-19,75
	Patients	918	1.120	1.004	978	1.153	841
	Variation (%)	+0,44	+22,00	-10,36	-2,59	+17,89	-27,06

From data in table 5, it's also possible to conclude that the decrease of 7,17% in the number of units and patients transfused with RBCs in 2020, when compared to 2019, is very small when taking into account all the challenges experienced in health care in 2020 due to the pandemic, in which there were limitations to care for non-COVID patients and also a low consumption of blood components by COVID patients.

As for the number of RBCs transfused per region, the proportion of distribution was similar to 2019, which in the same turn was similar to 2018, according to Escoval et al., 2020. When comparing the percentages of transfused RBC units with the percentages of total collected donations, for each region, in 2018, 2019 and 2020, as shown in table 6, it can be concluded that LVT has been the only region that is not self-sufficient, requiring more units and, consequently, the contribution of other regions of the country.

Table 6 – Percentages of transfused RBCs and collected donations per region, from 2018 to 2020 (adapted from Escoval et al. (2019), Escoval et al. (2020) and Escoval et al. (2021)).

Region		2018		2019		2020	
		Transfusion (RBCs)	Collection, with CSTs	Transfusion (RBCs)	Collection, with CSTs	Transfusion (RBCs)	Collection, with CSTs
Northern		31,06 %	41,67 %	31,14 %	42,79 %	31,57 %	42,09 %
Central		18,58 %	21,53 %	19,38 %	21,27 %	18,99 %	20,37 %
Southern	LVT	39,04 %	26,24 %	38,60 %	25,71 %	38,34 %	27,08 %
	Alentejo	3,90 %	22,25 %	3,93 %	22,07 %	3,86 %	23,44 %
	Algarve	18,58 %	21,75 %	3,65 %	21,33 %	4,06 %	23,31 %

Therefore, BSC management is important, specifically in the Southern region of Portugal, where there's more consumption while, at the same time, insufficient collected blood to meet the demand. Hence, the management of this limited number of products collected is key to assure that supply meets demand, with the minimum wastage of blood. Following this, the wastage of blood units in 2020 for RBC and PLT units can also be analyzed, by measuring the difference between produced units and transfused units, presented in table 7.

Table 7 – Production, transfusion and wastage data for RBC and PLT units, from 2018 to 2020 (adapted from Escoval et al. (2019), Escoval et al. (2020) and Escoval et al. (2021)).

Blood Product	2018			2019			2020		
	Prod.	Trans.	Wastage (%)	Prod.	Trans.	Wastage (%)	Prod.	Trans.	Wastage (%)
RBCs (WB)	303.060	290.001	4,30	297.693	293.892	1,28	276.857	272.811	1,46
PLTs (apheresis)	5.283	5.655	–	5.041	5.229	–	5.813	5.673	0,70
Pool of PLTs	35.369	30.456	13,89	29.064	27.138	6,63	15.005	19.256	–
Pool of PLTs (with PR)	3.134	2.936	6,32	9.987	7.885	21,05	21.640	14.214	34,32
PLTs (WB)	24.003	8.441	64,83	19.833	8.498	57,15	15.214	6.820	55,17

From analysis on table 7, it's clear that the units of PLTs, from WB, are the most wasted products, with more than half of produced units not being used over these years, which is of great concern. Then, the wastage of pools of PLT units with PR also stands out, with 34,32% of units being wasted in 2020. In 2019 the wastage trend was similar, and in 2018, wastage was even more significant for PLT units from WB, but less problematic for pools of PLT units with PR. However, even though a decreasing trend for wastage can be evidenced, it's not very significant, for any kind of wastage is bad and needs to be prevented.

2.5. Main problem characterization

The data on collection and transfusion presented previously suggests inefficiencies associated with these processes in the Portuguese BSC, resulting in a significant wastage of blood products.

Firstly, there's clearly an asymmetry in the donations by region and by hospital blood units, as the Northern region takes the majority of the national donations. Besides, differences are also presented in the number of collections performed by the hospital blood units, for some hospitals perform over 5000 collections per year and others about 1000 or less (Escoval et al., 2021). In terms of transfusions, it's clear that RBC units are the most demanded, presenting the highest number of transfusions and a low wastage throughout the years. However, PLTs and pools of PLTs, which are less demanded and less produced, present excessively high levels of waste. Additionally, in the LVT region there's an inability to meet the needs, as the quantities collected in this region aren't sufficient to meet the region's demand for transfusions, so the performed transfusions used units from other regions of Portugal. This exposes a clear imbalance between demand and supply in the Portuguese BSC, in the LVT region.

Moreover, the regional distribution of the CSTs can also contribute to these asymmetries, as the two largest CSTs are located in the north of Portugal (CSTP and CSTC) and only about 120 km apart, whereas the CSTL is more isolated in the south and almost 200 km and 300 km further away from CSTC and CSTP, respectively, not helping to an efficient management of the BSC by IPST, which strives to overcome these negative aspects.

To conclude, the presented disparities and inefficiencies from the Portuguese BSC need to be counterbalanced, with the use of new innovative approaches to possibly overcome the presented issues.

2.6. Main chapter conclusions

This chapter analyzed the case study for the Portuguese BSC that draws over IPST, the entity responsible for regulation and management of blood-related activities in Portugal. Firstly, the IPST's historical contextualization and organizational structure were described. Then, the Portuguese BSC was characterized by identifying and describing collection, processing and testing, storage and distribution as its 4 main stages, along with the facilities that participate in those stages – CSTs, hospital blood units, laboratories, mobile venues, etc. Later, the Portuguese BSC's performance was analyzed through data on collection and transfusion, from official records of IPST, reaching the conclusion that the Portuguese BSC faces some imbalances and inefficiencies, such as in terms of donations per region or per hospital, insufficiency to meet demand in the LVT region, and in terms of wastage, for over 50% of PLTs units are wasted. The problems identified support the added importance for an efficient and sustainable BSC management method, with the ability to fix the inefficiencies identified in the Portuguese case.

That said, this dissertation will make use of the analyses performed on this chapter and the main identified inefficiencies to conduct a literature review on BSCs and SCs of other perishable products, to then develop an innovative model focused on one of the problems identified in this chapter, and using data from IPST.

3. Blood supply chain and blood supply chain management

This chapter aims to review the existing literature on the BSC and BSC management, to further support the knowledge of what was discussed and reported in chapter 2 for the Portuguese case, and to identify what has already been made towards addressing the existing problems of the BSC. Firstly, section 3.1. conducts an overview on SC and SC management to help understanding the underlying concepts of the BSC. On the BSC, section 3.2. details the main features of the blood product., section 3.3. details the main literature reviews on BSCs and section 3.4. explains the two different network configurations that it can adopt - centralized and decentralized. Then, section 3.5. explains the main stages of the BSC, with subsections from 3.5.1 to 3.5.4 detailing each stage, collection, production, inventory and distribution, respectively. Further on, section 3.6. points out the main gaps and the most used methodologies in literature to optimize the BSC performance, and then section 3.7. presents the main problems, decisions, constraints, uncertainties and objectives for modelling the BSC. At the end, section 3.8. makes conclusions on this chapter.

3.1. Supply chain and supply chain management

A SC is a network that comprises several entities, a set of facilities and processes essential to its functioning with a certain service or product in common, which, as stated in section 1.1., is responsible for delivering the products in the right location, with the right quantity and at the right time (Barbosa-Póvoa, 2014). It corresponds to the entire process of making and selling the respective goods, including two main logistics, the internal, associated with processes related to materials management, such as supply, storage, manufacturing and shipment of finished goods, and the external, focused on the distribution to customers or clients, taking and processing orders, handling the inventory, outbound transportations, order consolidations and returns (Meneses, 2019).

Managing a SC is very complex, and gets even more complex as the number of entities, materials and information involved increases. SC management is the process that ensures a good performance of a SC by integrating the network facilities and stakeholders for coordinating information, material, and financial flows, in order to deliver value products to customers at the lowest possible cost and to meet their service level requirements, as stated in section 1.1. (Meneses et al. (2022) and Govindan et al. (2017)). SC management faces real challenges when making important decisions, which extend into 3 main hierarchical decision levels – strategic, tactical and operational. The strategic decision level incorporates long-term decisions, with a planning horizon of several years, with decisions related to the design and structure of the SC, such as the number of each type of facility, the respective location and the installed capacity, creating the foundation for the development of the SC in the future. The tactical level works on mid-term decisions, with a planning horizon ranging from a few months to one year, related to regular operations of the SC, usually made at an aggregate level, such as resources planning, inventory policies definition, transportation strategies and material flows. At last, the operational level includes short-term decisions, with a planning horizon between a few days and a few weeks, and focuses on day to day decisions for immediate execution, such as scheduling of production, selection of transport modes, definition of vehicle routes and human resources allocation. Of course, in this level, since the planning horizons shortens, more information is collected which means that higher accuracy regarding the uncertain parameters is demanded. Also, contrarily to the previous 2 levels, the operation level decisions focus on a much smaller network, or even a single facility from the SC (Barbosa-Póvoa (2014) and Meneses et al. (2022)).

3.2. Features of the blood product

Before advancing to the BSC and BSC management, it is important to provide some insights on the main features and characteristics of blood, such as the blood groups according to the ABO/Rh system, the possible substitutions for transfusion and the blood components and its specific characteristics.

Firstly, the ABO blood system classifies blood according to the presence of agglutinogens (also called antigens) on the surface of the RBCs, and agglutinins (also called antibodies) in the Plasma. Antigens are substances that can trigger the immune system to distinguish the body's own cells from foreign invaders that, if recognized, are destroyed by antibodies. In the blood's case, incompatibility occurs when someone with a certain agglutinin receives blood with the same agglutinogen, which triggers the donor's RBCs agglutination (i.e., the clumping of the RBCs bound together by antibodies), causing the block of small vessels and release of hemoglobin (Hb), which can block the kidney tubules of the transfusion's recipient and cause death (HealthEngine, 2008). Blood of type A has A antigens on the surface of the RBCs and anti-B antibodies in the Plasma, and blood of type B has B antigens on the surface of the RBCs and anti-A antibodies in the Plasma. Blood of type AB has both A and B antigens on the surface of the RBCs, and no antibodies in the Plasma, and blood of type O has no antigens on the surface of the RBCs, and both anti-A and anti-B antibodies in the Plasma (American Red Cross, 2020). As for the Rhesus system, it 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. Then, the Rh system gives rise to two types of blood – Rh positive or Rh negative. The Rh- blood types lack the Rh antigen, so if given transfusion of Rh+ blood, the immune system responds by producing anti-Rh antibodies. If Rh+ blood is again transfused, the previously produced anti-Rh antibodies will attack the foreign RBCs, causing their agglutination and consequent hemolysis (Britannica, 2020).

So, the ABO/Rh blood classification identifies 8 blood types (A+, A-, B+, B-, AB+, AB-, O+ and O-). In order to avoid adverse reactions from transfusions, it's important to know the blood types of the donor and the recipient before transfusion. Usually, the recipient is transfused with the same blood type. However, in case of shortage of a specific blood type, it is also important to know the compatibilities and the preference orders for the possible substitutions, which are as follows in table 8.

Table 8 – 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)).

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

Even if blood types are compatible, they have different priorities for substitution. Table 8 shows the RBCs compatibility according to the ABO/Rh blood system, and by which it's possible to see that individuals with O- blood type are universal donors, being this the most wanted type of blood in situations of emergency, such as, for example, when the recipient's blood type is not yet known and a transfusion is urgently needed. On the other hand, individuals with AB+ blood type are universal recipients. As for the preference order for substitutions, taking the example of AB+ blood type, the table shows that even if its demand can be met by all other blood types, AB- and B+, respectively, are the 2 highest prioritized blood types.

In a transfusion, the blood products transfused from a donor to a compatible recipient can be either the WB or separated blood components. The blood's 4 main components are Plasma, RBCs, white blood cells, and PLTs. Plasma is a mixture of water, sugar, fat, protein, and salts, that accounts for about 55% of the blood's volume, and its main job is to transport blood cells throughout the body along with nutrients, wastes, antibodies, clotting proteins, etc. RBCs, or erythrocytes, account for 45% of the blood's volume, and contain the hemoglobin protein responsible for carrying the oxygen from the lungs to the rest of the body and returning the carbon dioxide to the lungs to be exhaled. White blood cells, also called leukocytes, account for only about 1% of the blood's volume, and are responsible for the protection of the body against infections. At last, PLTs, or thrombocytes, that account for less than 1% of the blood's volume, help the coagulation process at the site of injury (ASH, 2009).

Table 9 – Characteristics of the main blood products (adapted from Pirabán et al. (2019)).

Blood product	SL	Storage conditions	Main uses
WB	21/35 days (depending on the anticoagulant used)	18 to 24 ºC	Trauma and surgery
RBCs	42 days (depending on the anticoagulant used)	2 to 10 ºC	Trauma, surgery, anemia and blood loss
PLTs	3 to 7 days	20 to 24 ºC (with constant agitation)	Cancer treatments and organ transplants
Plasma	1 year	≤ -30 ºC	Burn patients and bleeding disorders
Cryo	1 year	≤ -30 ºC	Hemophilia and Von Willebrand disease (blood clotting disorder)

Following this, when blood is donated, 2 collection methods can be used: WB or apheresis, in which blood's specific components – RBCs, PLTs, Plasma and/or Cryo – are obtained separately. Each of these specific blood components has its own characteristics, such as SL, storage conditions and main uses, as detailed in table 9, which gathers the main characteristics of these components.

Since the separation of the WB into its components requires specific and dedicated equipment and facilities, developed countries are expected to have better conditions for this collection method. In fact, according to the World Health Organization (2020), in developed countries 97% of WB donations are separated into components, while in developing countries only 37% of WB donations are separated into components. Moreover, other significant disparities exist between developed and developing countries besides the previous, such as the number of donations and therapeutic applications of transfusions, for, also according to the World Health Organization (2020), 40% of total donations in the world are from developed countries and are used for advanced medical procedures.

3.3. The blood supply chain, a literature review

The BSC starts with the donors, at collection points, and ends with the patients, at transfusion points. Hence, the management of the BSC is responsible for managing the flow of blood through the constituent steps of the BSC so as to ensure the availability of blood products where and when they are required for transfusion, while avoiding at maximum their wastage.

Therefore, given its importance, the BSC has motivated researchers since 1960, with a significant part of the literature developed in the 1970s and 1980s, covering distinct aspects of the BSC (Osorio et al., 2015). The early work of Jennings (1973) was the first framework to classify the WB inventory problem, presenting it by hierarchical level and showing the impact of different blood inventory policies. In the 1980s, Nahmias (1982) performed a complete overview of the theoretical models in perishable inventory, according to features such as the type of demand or type of lifetime of the products. Later, other review articles focused more on specific blood products, such as Blake (2010) and Stanger et al. (2012) for PLTs and RBCs, respectively. In the 20th century it was also when researchers started to analyze the whole SC, describing advances and opportunities for further research, such as Pierskalla (2005), which broadly analyzed different network configurations, locations, allocation and distribution decisions, and Lowalekar & Ravichandran (2014), that gave a general overview of the state of the art of blood banks in India.

Nevertheless, 4 main reviews on the BSC are identified, 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. This review classifies the existing models into 8 classification fields, highlighting for each of them the most important contributions, identifying recent trends and indicating which areas should be subjected to future research. The 8 fields considered, and conclusions on future research for each one, are the following: 1) Type of blood product: the authors distinguish between WB, RBCs, PLTs, Plasma and frozen blood, and conclude that there is a peak in publications on RBCs and PLTs, and that PLTs can be a fruitful area for further research; 2) Solution method: simulation is the most frequently used quantitative approach to problems, and recent research tends to emphasize that the application of methodologies from different fields, such as econometrics, database management or operations management, will make part of the multidisciplinary aspect of the BSC management, rather than sophisticated linear (integer) programming or dynamic programming models without a decision support model system; 3) Hierarchical level: the literature is classified at 3 levels – individual hospital level, regional BC level and SC level – reaching the conclusion that the last level was hardly studied before 2000, only catching up with the other 2 levels in the last decade; 4) Type of problem: the authors distinguish between inbound problems (inventory and planning problems) and outbound problems (distribution, scheduling and supply problems), concluding that inbound problems are more extensively mentioned in the literature; 5) Type of approach: between stochastic and deterministic approaches, the stochastic ones, which underlie with uncertainty, are privileged over the deterministic ones; 6) Exact versus heuristic: it is hard to forecast which approach will receive the most attention in the near future, since there is an almost equal focus on exact solution methods and heuristics; 7) Performance measures: safety and quality are only mentioned in literature since 2005, and are still less studied than outdates, shortages, availabilities and transportation issues; 8) Practical implementation/case studies: there is a trend towards practical case studies, and the authors forecast that in the future literature on real-life data and/or implementations will outnumber literature on nonpractical testing.

The second main review on BSC is from Osorio et al. (2015), which perform 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. The authors break the models into 5 categories, the first 4 representing the four echelons/stages of the BSC – collection, production, inventory and distribution, as illustrated in figure 4 –, and the fifth containing models that integrate those 4 echelons. For each category, the authors make a diagrammatic element representing all the decisions and relationships by hierarchical level, and give a description of the main features, contributions and gaps found in the analyzed models. From this review, the authors conclude that there is a renewed interest in research for this topic, but with the following still poorly addressed: 1) collection alternatives, optimization of costs and planning considerations; 2) allocation of donors to collection processes; 3) product allocation among facilities, application of blood transshipment and ABO/Rh-substitution; 4) blood products' production alternatives; 5) the simultaneous consideration of different blood products and the influence of reducing their SLs; 6) the achievement of optimal policies for blood products; 7) supply constraints in inventory policies; 8) reflect indicators of donors required to meet demand; and 9) the simultaneous addition of inventory features, such as the crossmatching rate, release period and mismatching (Torrado & Barbosa-Póvoa, 2022). In addition, the authors refer an existent significant gap in integrating the entire BSC flow and that most literature focuses on one single echelon, which can lead to a myopic view of the BSC. From this, the authors conclude that there is a clear need for modelling the entire process flow in the BSC, which can help to identify bottlenecks, evaluate policies from a whole-system perspective, and recognize constraints in preceding and succeeding echelons.

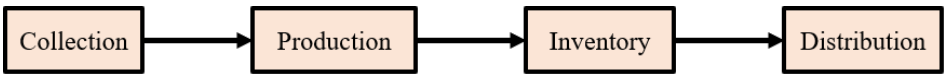

Figure 4 – Echelons of the BSC, according to Osorio et al. (2015).

More recently, Pirabán et al. (2019) explore BSC studies from 2005 to 2019, highlighting research gaps and interesting directions for future works. The authors investigate the reference papers in terms of 5 categories: 1) Decision-making and forecasting environments; 2) Issues in the design of the BSC; 3) Operational processes and planning decisions; 4) Modeling and solution methods; and 5) Data characteristics. Contrarily to Osorio et al. (2015), which used a process-based definition of echelon, this review adopts a facility-based definition of echelon, where each echelon is constituted by a set of facilities performing similar functions (Govindan et al., 2017). Hence, the authors design the BSC considering 5 echelons, as illustrated in figure 5: Donors, Mobile CSs, BCs, DNs and Patients.

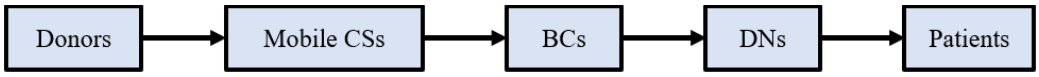

Figure 5 – Echelons of the BSC, according to Pirabán et al. (2019).

Still, the 4 echelons identified by Osorio et al. (2015) are incorporated in the BSC echelons drawn by Pirabán et al. (2019). After the arrival of the Donors, at the Mobile CSs, there is both collection and transportation to BCs. At the BCs, collection, production, storage and distribution are performed. At the DNs, blood is stored in unassigned inventory and crossmatching tests are performed. Reaching the Patients, the crossmatched products are stored in assigned inventory to then be transfused. All these processes are further described and discussed in section 3.5.

Following this, Pirabán et al. (2019) also highlight drawbacks, gaps and potential directions for the future, such as the use of machine learning algorithms or big data analysis, and describe the need for the consideration of useful practices to manage data, complex configurations under an uncertain environment, and efficient solution approaches to deal with complexity. Furthermore, the authors mention the need for: forecasting environments based on an estimation of supply and demand; new algorithms to study the donors and non-donors; the comprehensive study of the multiple echelons and respective interactions among them; studying the uncertainty effect on the SC; design collection policies to avoid inventory levels from surpassing the demand; new alternatives for delivery vehicles, such as drones, for urgent situations; the exploring of the testing and processing phases; the study of the allocation of staff and resources; and the use of efficient and effective solution methods (Torrado & Barbosa-Póvoa, 2022).

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 authors narrow down the group of problems outlined from the literature to nine major problems, and classify them in 3 dimensions, as stated: "the planning level, which divides decisions according to the length of the planning horizon and the level of detail required in three different levels (strategic, tactical, and operational level); the main processes (collection, production, storage, and distribution) and the main facilities involved (CSs, BCs and DNs)". Moreover, the authors, which follow an integrated perspective of the BSC, demonstrate how tactical-planning decisions are integrated with the strategic and operational planning levels, and conclude that decomposing the problem helps to handle the complexity of the BSC management, by considering the interdependencies between the planning tasks. Thus, one of the main literature gaps identified by the authors is the limited consideration of the full integration of BSC decisions from the three planning levels in a single model.

3.4. The blood supply chain network configuration

Finding the optimal network configuration for the BSCs is a highly challenging problem, that must address production factors, collection strategies and economic, political, geographical and even cultural considerations. There are extended collection and separation alternatives, different geographical conditions and different costs, which condition demand for the blood products, the availability of donations, product compatibility and also collection and production alternatives. Following this, the BSCs can be configurated 2 ways, either centralized or decentralized, as according to Osorio et al. (2018).

Centralized systems are composed by regional divisions with several coordinated and interdependent blood facilities, that operate under the authority and administration of top management. In other words, there is a Regional BC in each geographic area which is in charge of the coordination and administration of its lower-level units, the DNs (Nagurney et al., 2012). These systems predominate in developed countries, such as the United Kingdom, or Portugal as it was described in chapter 2, and carry economies of scale as positive influences, which allow significant cost savings, along with a better performance to meet the supply needs of each region's DNs, with lower outdated rates and lower overhead costs. On the other hand, these systems require specialized labour to handle large quantities of products.

Contrarily, decentralized systems have many dedicated and independent blood facilities that govern themselves and decide on their operating policies, and are more common in developing countries, like Colombia. These systems

are less complex than centralized systems but may require trained staff on remote or rural areas, which can be difficult to find. However, large distances between blood facilities and DNs, which consequently increases the transportation costs, and geographic remoteness, which negatively influences the number of donations collected and increases the risk of stock disruption, are risks that can be attenuated by a great and significant number of blood facilities, which in turn also contribute to local economic development and generate employment opportunities within regions (Osorio et al. (2018) and Francisco (2021)).

3.5. The blood supply chain stages

According to the process-based definition of echelons, from Osorio et al. (2015), the terminology adopted for this section follows the 4 main stages identified by the authors for the BSC network – collection, production, inventory and distribution.

3.5.1. Collection

The first stage is collection, which comprises the processes of procurement of blood and blood products. It is responsible for obtaining, from donations, the quantity of blood and blood products needed to satisfy the demand for blood products and feed the rest of the network.

Typically, blood is collected at fixed or mobile donor centers, and then transported back to a processing and testing facility, usually a BC, and is stored there awaiting onward distribution (Osorio et al., 2015). Donations can be either from schedules or walk-in donors at the collection locations, and the appointment decisions, according to Alfonso et al. (2013) and Özener et al. (2019), consist of the duration according to the method used and the time slots during the day for that respective method. Also, and as according to Alfonso et al. (2013), the collection stage can be divided into 4 phases, each requiring resources and specialized staff, such as secretaries, physicians and nurses: 1) The reception and registration of (potential) donors; 2) Clinical and physical exams, such as weight, blood pressure and Hb concentration, to determine if the donor can proceed with the donation or not; 3) The donation/collection itself; 4) Donors take a light meal while receiving post-donation supervision.

There are 2 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, and extracted into satellite bags: double bags for RBCs and Plasma, triple bags for RBCs, PLTs/Cryo and Plasma, or quadruple bags for RBCs, Plasma and buffy coat (PLTs and white blood cells). Apheresis is a method that extracts one or more specific isolated blood components (RBCs, PLTs or Plasma) into separated bags, and returns the remaining blood to the donor (Osorio et al. (2015) and Pirabán et al. (2019)). These 2 methods differ in the blood products obtained, in efficiency, frequency, duration and even costs, which include collection bags costs, staff costs, machine utilization costs and operational costs of each phase of the collection process. The yield of blood products by apheresis is considerably 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 (Pirabán et al., 2019). In addition, these 2 collection methods also differ in terms of the CSs in which they can be performed. There are two types of CSs, that contrast in costs, locations, capacity

and functions: fixed or temporary CSs. Fixed CSs include BCs 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 latter are vans or caravans permanently equipped with the necessary material for blood collection that travel to various locations, although per day the number of locations it can visit is limited. The mobile venues must be public locations, such as governmental organizations, municipalities or universities. (Pirabán et al., 2019 and Francisco, 2021). The greatest difference between fixed and temporary CSs is the location, as the temporary sites can move between geographic regions and the location of fixed sites cannot be changed, being defined in the long term. However, fixed sites offer a greater capacity for blood products and staff, and more equipment, which implies higher establishment costs. As for the functions, fixed sites are responsible for contacting the donors and setting collection targets and mobile venues are responsible for contacting other entities for scheduling the collection sessions, whereas for bloodmobiles it is the top management that makes decisions (Gunpinar & Centeno (2016) and Şahinyazan et al. (2015)).

Following this, decisions on the collection stage mainly refer to location and capacity decisions, collection methods and donor management. Strategic, long-term decisions, which will affect the lower levels of decisions, include the definition of the locations of CSs, the definition of capacity and the definition of staff. Tactical, mid-term decisions include the definition of policies, the planning of collection campaigns and the allocation of staff to collection points. And operational, short-term decisions include the scheduling of collections, the collection methods to use according to each donor, and which routes to take for collections (Osorio et al., 2015).

According to Pirabán et al. (2019), there are several problems identified in the literature with the collection process, such as defining the right quantity of blood to collect from donors and which collection methods to use, forecasting the supply by estimating the arrival of donors, their motivation and behavior, defining the optimal fleet size of bloodmobiles along with its visit durations and frequency, allocating staff and resources and estimating the collection costs. Defining the collection policies is also very important and a challenging task. There are 2 possible collection policies to reduce wastage of blood stemming from overcollection scenarios, as considered in literature by Lowalekar & Ravichandran (2010) that compared them in terms of shortage, wastage and total costs. The first is the unrestricted collection policy, which consists of collecting all available quantity of blood from all donors. The second is the cut-off level policy, in which a fixed quantity of blood is collected to meet the target inventory, or in which it is collected the quantity equal to the difference between the target inventory and the stock level immediately before collection. The authors concluded that the cut-off policy must be carefully established to maintain a certain demand fill rate, but, however, it outperformed the unrestricted collection policy, controlling the total costs and wastage for a given level of shortages.

To conclude, the collection process faces some serious challenges, that can compromise the performance of the BSC. It is the first stage of the network, being very important as it carries the responsibility of collecting the donated blood and blood products to meet demand and feed the rest of the network. According to Osorio et al. (2015), the different collection alternatives, costs optimization, the location of mobile centers and the consideration of periodicity

for regular donors, are still unaddressed areas in the literature up to 2014, which, if addressed could improve the process and attenuate related problems. Moreover, the collection capacity and costs, donation time, the maximum sites to visit by bloodmobiles in a period, the delays between bloodmobile visits, the operation hours of the CSs and working time of staff, the discarded products and the probability of donor deferral, amongst other areas identified in the literature by Pirabán (2019), should be analyzed and studied for the collection process.

3.5.2. Production

Production is the stage where blood is received after collection at the BCs to be tested and then possibly fractionated, meaning, broken down into RBCs, PLTs, Plasma and/or Cryo (Osorio et al., 2015).

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. In addition, different sets of screening tests can be selected, considering the infection prevalence rates of the donors (Pirabán et al. (2019) and Nagurney et al. (2012)). From the existent literature, Pirabán et al. (2019) identifies the testing process main problems, such as the percentage of products discarded by testing, the set of tests to apply and the estimation of testing costs, as well as the important parameters to measure in this stage, such as the discarded units, the testing capacity and costs, the age limit for testing, the budget to administrate screening and the true negative/positive probability of the tests.

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 (Osorio et al., 2018). Separating large amounts of WB into components may be beneficial for patients, but not necessarily optimal for the BCs, since it increases holding, processing and wastage costs, meaning that the optimal amount of fresh WB to be fractionated should be previously studied (Pirabán et al., 2019). Following this, Pirabán et al. (2019), from the reviewed literature, identifies the quantity of blood to process and the estimation of the processing costs to be the main problems for the processing process, and the processing costs and capacity, the proportion of products obtained from WB, the processing/yield loss cost, the age limit for processing, the profit of the BC per product and the fractionation machine purchasing cost as important parameters to measure at this stage of the BSC.

To conclude, decisions on this stage, as identified by Osorio et al. (2015), are mainly related to how to explore the fractionation alternatives and the advantages of the collection methods to improve the performance of the BSC. The strategic, long-term decisions include the determination of locations and capacities of the CSs, which are not easily reversible. The tactical, mid-term decisions include the staff allocation, the production master planning and the definition of the facilities' layout. Finally, operational, short-term decisions include the daily planning, such as scheduling of staff, paths for blood fractionation, timetabling and scheduling for testing.

3.5.3. Inventory

Mainly due to the short SL of blood products, inventory is the BSC stage that has received the most attention in the literature, for since the 1960s, researchers began to develop new methodologies to study inventory policies for blood products.

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. On this hand, managing the storage of blood involves setting the appropriate policies to guarantee the sufficient availability of the diverse blood products to meet demand for the BSC, when and where they are needed along the network (Francisco, 2021).

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 Osorio et al. (2017). 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). For the (*R*,*Q*) and (*R*,*S*) policies, in every *R* time a fixed quantity *Q* is ordered or a variable quantity sufficient to raise the stock level to a target *S* is ordered, respectively. For the (*R*,*s*,*S*) policy, an order is only performed if the current stock falls below the safety stock *s*. Continuous policies, less used, include the (*s*,*Q*) and (*s*,*S*) control policies, which contrarily to the previous ones assume continuous review. Whenever the current stock position falls below the safety stock *s*, then a fixed quantity *Q* is ordered, for the (*s*,*Q*) policy, or a variable quantity sufficient to raise the stock to the target level *S* is placed, for the (*s*,*S*) policy (Dillon et al., 2017). In fact, Osorio et al. (2017) and Osorio et al. (2018) argue that BCs should define a minimal safety stock *s* for each blood product, proportional to the variability of demand for each, and that a dispatching rule should be applied, saying that for each day and blood product, the maximum quantity that can be dispatched is equal to the difference between the total inventory on hand and the safety stock *s*. According to Duan & Liao (2014) and Osorio et al. (2017), 1-day is the most common period review policy in BSCs, with the advantage of allowing the coordination of inventory replenishment with distribution, which often occurs daily. With this 1-day period, at the time of review the outdated units are removed for incineration, the residual SL of the remaining units is shortened by one day and the newly received units are added. Blake et al. (2013) also studied the 1-day period policy in DNs, with the orders sent to BCs at the end of the day, which are oftentimes combination orders aimed at replenishing the inventory depleted plus the emergency orders. The authors also acknowledge the common practice of BCs to dispatch the orders over night, in order for blood products to be received by the DNs early in the morning, with an almost instant replenishment and an approximate null lead time (the time between the realization and the arrival of the order).

More on review policies, Broekmeulen & van Donselaar (2009) introduced the EWA (Estimated Withdrawal and Aging) replenishment policy, that consists in subtracting the estimated value of waste due to outdating from the quantity of inventory available, thus having a more realistic value of the quantity that will be in inventory. This policy takes into account all information about the age distribution and the assumptions on the withdrawal policy and the inventory system are different from the previously described policies. Besides, it assumes a constant safety stock, which does not use information on the demand distribution other than the expected demand. Duan & Liao (2013) also proposed another periodical inventory policy, the OIR (Old Inventory Ratio) policy, where the production quantity is firstly determined according to the original Order-To-Up-Level (*R*,*S*) level, which only accounts for the number of items on stock. Then, the proportion of "old" items (whose residual SL expires in one to three days) to the total items on hand is calculated. If it exceeds a certain threshold level, an additional replenishment, with size equal to the total

number of the "old" items at the time of the review, is triggered to account for the possible outdating caused by the "old" items, guarding against possible wastage. The authors conclude that the advantage of OIR against the EWA policy is that the same performance can be achieved using less information about the ages of the inventory. Moreover, Rajendran & Ravindran (2017) tried to minimize wastage using a stochastic integer programming model under demand uncertainty that aimed to determine the number of PLT units that DNs should order and when. The authors proposed three innovative ordering policies and then compared them with the (*R*,*S*) policy: 1) Modified Order-To-Up-Level policy (*R*,*S´*), that considers the coefficient of demand variation (the ratio between the standard deviation and the mean of the demand) and defines *S'* as the desired inventory level, which is a multiple of the average demand during the lead time and the review period; 2) Weighted mean-variance policy, that considers the weighted average of demand and the standard deviation over several periods; and 3) Last value policy, where the quantity ordered at the end of the day equals the sum of the demand during that day and the demand during lead time plus review period. The authors concluded that (2) and (1) are the best policies in case the demand variability is low or high, respectively, and that (3) is the most appropriate policy if the inventory storage capacity of the DNs is low.

Blood issuance policies are also set in this stage. The 3 main issuing policies 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 (Pirabán et al., 2019). Abdulwahab & Wahab (2014) studied hospital PLT banks and stated that FIFO is the optimal issuing policy, minimizing shortages, outdated units, and average inventories. Also, as stated by Blake et al. (2013), at the BCs, the FIFO orders are processed in batches according to the average daily demand of the DNs, which means that the DNs with higher average daily demand receive the oldest blood products, with lower residual SL, whereas the DNs with lower average daily demand receive the most newly stored blood products, which helps to prevent wastage.

Inventory can be of 2 types, assigned and unassigned, as firstly studied back in the late 1960s by Jennings (1968). Later, more articles and reviews started to approach these concepts as well. 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 (Pirabán et al., 2019). According to Osorio et al. (2015), 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). This should be as short as possible, so that most of the units in the assigned inventory are transferred and, if not, moved as quickly as possible to the unassigned inventory. The C/T ratio is also important to analyze at this stage and that should be as close as possible to 1, preventing wastage (Duan & Liao, 2014). In addition, double crossmatching tests can also be performed, where blood units are reserved and available for two patients while ensuring if both need to be transfused. Using this kind of tests increases the likelihood that assigned inventory units will be used, minimizing the unused assigned units (Beliën & Forcé, 2012). However, both single and double crossmatching tests imply the existence of the two types of inventory, assigned and unassigned, and surgical reserves should be managed without constituting assigned inventory. Hence, Pereira (2005) evaluated an alternative to crossmatching, called Type & Screen

(or electronic crossmatching), a method for inventory management in DNs that relies on only one inventory. In this case, the only blood inventory in the DNs corresponds to the previous unassigned inventory. If a transfusion is needed, then a blood unit is issued from the available inventory, whose compatibility according to the ABO/Rh blood group is already known in advance. The author concluded that this method outperforms crossmatching, although until 2005 not being completely accepted by medical staff (Osorio et al., 2015).

The assigned inventory of blood to patients, the perishability of the blood products (specially for PLTs which have the shortest SL) and other special features, such as crossmatching and mismatching, increase the complexity of the blood inventory management, which has stimulated many theoretical developments in this area (Osorio et al. (2015) and Pirabán et al., (2019)).

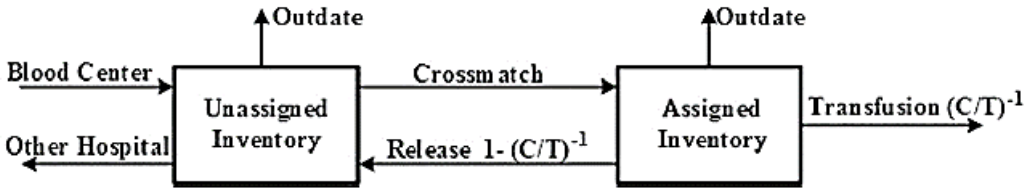

Figure 6 – Blood transfusion process in a hospital blood bank. Source: Najafi et al. (2017).

Following this, decisions on the inventory stage mainly relate with the definition of the inventory policies. Strategic, long-term decisions include the network design, location decisions, and what information systems to use. Tactical, mid-term decisions include the definition of inventory policies, staff allocation, mismatching and crossmatching policies. And operational, short-term decisions include the daily quantities to order, how to meet special orders, such as in emergencies, and what specific products should be issued (Osorio et al., 2015). These decisions from inventory management have to ensure the minimum of shortages and wastage, at the lowest possible total cost. The inventory-related costs include ordering, holding, shortage and wastage costs (Dillon et al., 2017). Holding costs represent the costs associated with storing the blood products while guaranteeing all appropriate conditions, such as refrigeration (Dillon et al., 2017). Shortage costs, which occurs when a BC or DN does not have sufficient stock to meet demand, include short-term production, emergency deliveries or getting blood from other BCs through import/export functions (Civelek et al. (2015) and Haijema et al. (2007)). Wastage costs consider the total effort spent in manufacturing each blood product and the additional disposal processing (Custer et al., 2005).

Following this, the main problems with inventory management, as identified by Pirabán et al. (2019), are the following: inventory and issuing policies, the quantity of blood products to order by the DNs, the effects of reducing the maximum SL of blood products and the remaining SL of the blood products arriving at the DNs, the crossmatch release period, assigned inventory, factors that affect wastage of blood, the C/T ratio and the estimation of the holding costs. The authors also identify important parameters to measure and evaluate in inventory management, particularly: holding, shortage and wastage costs, the storage capacity of the DNs and the BCs, the percentage of outdated products, the crossmatch release period and the time taken for crossmatching tests, ordering and shipping costs, assigned inventory, the C/T ratio, and the maximum shortage, maximum wastage and minimum inventory levels.

3.5.4. Distribution

Distribution, the last stage of the BSC, happens whenever there is movement of blood and blood products between facilities in the BSC. Hence, it involves 2 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 (Francisco, 2021).

The 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. After this last process, the vehicles can pick up unused blood products from the DNs and collect fresh blood from the mobile venues and the bloodmobiles during the return journey to the BC. Shuttles are used to assist the mobile venues and bloodmobiles, supplying them with necessary and additional resources, once that these only return to the BC at the end of the planned horizon and might need support throughout that time, so they do not have to return to the BC every day. Shuttles also pick up and deliver collected WB from mobile venues to the BCs in regular intervals because the WB donations for PLT and Cryo separation have a processing time limit of 6 hours, which is the maximum time interval during which WB can remain at room temperature conditions without compromising its quality (Pirabán et al., 2019). To study the minimum number of pickups the vehicles should make for each collection location, Doerner et al (2008) addressed the vehicle routing problem with multiple interdependent time windows. The authors developed tools to find the minimum cost routes and allocate the appropriate vehicles to those routes, minimizing the total driving time, reaching the conclusion that increasing the number of pickups at the selected CSs beyond the theoretical minimum number of pickups has a great potential for reducing costs.

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. According to Wang & Ma (2015), Lateral Transshipment is relevant when there is insufficient supply, limited SL of products, uncertain demand and supply and high service level requirements, presenting two advantages according to Dehghani et al. (2021) and Paterson et al. (2011), respectively: to enhance the flexibility of the BSC network, as it balances stock among the facilities by reallocating inventory, and to allow facilities to pool their inventories and reduce the safety stock levels, minimizing inventory holding costs whilst maintaining the required service level. Also, as according to these last authors, Lateral Transshipment can be divided into Proactive or Reactive Lateral Transshipment, the first occurring at predetermined moments before demand is realized and the second when shortage is realized, acting quickly and effectively to relieve the supply pressure of the DNs. In fact, Lee et al. (2007) studied the Service Level Adjustment policy, which combines these two processes and relies on service level to decide what quantity should be transshipped in case of shortage, reaching the conclusion that this policy has lower total costs and responds more effectively to changes in demand. More recently, Dehghani & Abbasi (2018) from a study in which the smaller DNs (with smaller average daily demand) transship older units to larger DNs (with greater demand), concluded that placing emergency orders whenever a DN is in stockout is costly, and that the Reactive Transshipment policy can help saving these costs and improve the average age of the transfused blood. Later, Dehghani et al. (2021) used a stochastic programing model, with uncertain demand, to understand how the Proactive Transshipment policy could prevent shortage and minimize wastage, by calculating the optimal order quantities to transship to minimize the total costs. The authors concluded

that this policy brings cost benefits, namely by reducing the safety stock levels and wastage of blood. Distribution costs mainly cover the drivers' salaries, fuel costs, maintenance expenses and amortization costs (Duan & Liao, 2013).

At this stage, Osorio et al. (2015) identifies decisions mainly related to the process of transporting the blood products from the inventories in BCs to the hospitals to be transfused to patients. Strategic, long-term decisions include the product delivery, such as choosing the types of vehicles or defining their capacity and staff. Tactical, mid-term decisions, include routing and allocation of the vehicles. And finally operational, short-term decisions include the scheduling of vehicles, packing, transshipments between different locations and meeting time window constraints.

According to the literature reviewed by Pirabán et al. (2019), the main problems and planning decisions associated with this stage include the selection of transportation links, the locations, the quantities of blood products shipped by the transportation links, the routes and the activity frequency between echelons. Additionally, important parameters to measure at this stage, identified by the authors, include the transportation costs, travel times, distances, opening costs of facilities, capacity of the locations, the coverage radius, the trips' distances and durations limits, along with the carbon emissions.

After blood products are distributed and stored at the DNs, Transfusion is performed. At this process, a patient should be transfused with his/her own blood type. However, when the matching blood type is not available at the time of request, then a compatible group must be provided, according to the ABO/Rh compatibilities and preferences, as mentioned at section 3.2., in table 8. Katsaliaki (2008) argued that using ABO/Rh-mismatched products was medically perceived as poor quality service, not recommending it. But, later and conversely, Duan & Liao (2014) concluded that using compatible blood types when needed provides more flexibility in the inventory management and prevents unnecessary outdated units, whilst offering a second chance to match the demand with supply more effectively. Another feature related to Transfusion is the age-dependent demand, which is based on the hypothesis that the freshness of the blood products may be critical and required for certain types of patients. Civelek et al. (2015) proposed using a protection level to limit age-substitutions and defined 2 types of patients, type 1 who require young blood and type 2 who can receive any age blood. Years before, Atkinson et al. (2012) also proposed a 4 option method to determine what kind of blood a patient should receive, as follows, ordered from the most to the least preferred and considering a target age α: 1) the oldest products of the exact blood type and younger than α; 2) the youngest product of the exact blood type and older than α; 3) the oldest product of a compatible type and younger than α; 4) the youngest product of a compatible type and older than α.

To conclude, Pirabán et al. (2019) identifies in literature the main problems with the Transfusion process as the demand forecasting, the distribution of blood types forecasting and the delays. The main important parameters to measure from this process, the same authors identify them as the distribution of the blood types, the costs of ABO/Rh substitution, the minimum service level and the costs of delays.

3.6. Main gaps and methodologies from literature

In each stage described previously in section 3.5. there are some matters which have been rarely studied, as follows, according to Osorio et. al. (2015) and Pirabán et al. (2019). As 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. From the latter, recent articles highly focus on PLT concentrates. Yet, the question of the ABO/Rh-substitution products has few research, although being an inherent feature of the BSC, as well as questions on centralized vs decentralized inventory and the allocation of staff and resources along the network. Lastly, the distribution stage problems, such as product allocation to the production centers and collaborative schemes, are not very addressed and need more attention. Furthermore, the use of shuttles is also scarcely studied in literature, as these vehicles could be extended to making multi-trips and guarantee the arrival of fresher blood to the BCs. In addition, and as mentioned previously at section 3.3., Meneses et. al (2022) conclude that there is few literature dealing with the entire model and the connections and interrelations between the multi-echelons and the three main planning levels. 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 (Osorio et al. (2015) and Pirabán et al. (2019)).

Regarding the main methodologies used in literature, most approach the uncertainty of the BSC parameters. Hence, mathematical optimization techniques are frequently applied in the literature as methods to address BSC problems, defining the parameters of the whole SC. These environments can be either stochastic, the most common, where the probability distributions of uncertain parameters are known and described by either continuous or discrete functions, unknown, where there is no information about the probability distributions of the random parameters, or fuzzy, where the random parameters are considered as fuzzy numbers.

The most approached methods for modelling stochastic problems used in the literature include Stochastic Programming (SP), Chance Constraint Programming (CCP) and Two-stage SP (TSSP). Markov Decision Processes and Queuing Models are other mentioned methods in the literature, but much less used (Pirabán et el., 2019).

SP finds the optimal decision for problems with at least 1 parameter modeled as a random variable (Pirabán et al., 2019). As mentioned in section 3.5.4. this method was used by Dehghani et al. (2021) and by Gunpinar & Centeno (2015). The latter, considering a 2-level BSC consisting of one hospital and one BC, tried to determine the optimal quantity of RBCs and PLT concentrates to order to minimize shortage, wastage and total costs, considering the age of the blood units in inventory, the demand for the 2 different types of patients (urgent vs non-urgent) and the uncertain nature of the demand. The C/T ratio and the crossmatch release period, unique characteristics of the BSC, were also taken into consideration. They concluded the following: for the age of blood units, the higher the average age of the units received, the higher the wastage; for the C/T ratio, the higher the ratio, the higher the number of units returned to unassigned inventory and, so, the higher the wastage; for the crossmatch release period, the higher the period, the longer units spend in assigned inventory and, so, as the life span of units decreases, the higher the wastage.

CCP assumes uncertainty in a constraint stating that it should be satisfied with a pre-specified probability (Govindan et al., 2017). This technique was used by Najafi et al. (2017), that developed a mathematical model to manage blood ordering and issuing, accounting for the uncertainty in blood demand and supply, the possibility of blood transshipment, two types of demand (fresh and old blood) and considering blood types substitution to minimize shortage and wastage. The authors used the CCP technique to develop a deterministic counterpart for the proposed

model to remove the uncertainties, creating non-linearity, so the model was then adapted to include approximations. From a numerical study on the model, the results showed that the use of a lower transshipment value threshold decreases outdates, and that a higher C/T ratio leads to a further reduction in shortage and wastage.

TSSP is a method that views data as random. In this method, the first-stage decisions are taken without full information on random data, and then the full information is received and second-stage decisions or corrective actions are taken. With this technique, a greater number of possible scenarios makes a more precise representation of the stochastic process, but more computational effort is required. This was used by Dillon et al. (2017), that aimed to define an optimal (*R*,*S*) inventory control policy for the BSC based on periodic review, more precisely for RBCs, finding the optimal time between the inventory reviews *R* and the target inventory level *S* that should be used as reference for defining order quantities. It focused on minimizing operational costs and shortage and wastage due to outdating. By using a TSSP model, the authors took into account the perishability of the products while representing the complex stochastic nature of the product's demand. In the first stage, the authors proposed a novel TSSP model for defining the optimal (*R*,*S*) periodic review policy considering the uncertainty and product perishability, and in the second stage they illustrated how the proposed framework could be used in reality by presenting a case study that leads to meaningful insights on how the RBC inventory management activity could benefit from its use. The conclusions indicate that it seems to be possible to modify the current policy by reducing the ordering reference point *S*, without compromising the service provided and while minimizing outdate, age of issue and holding costs, and that considering multiple blood types and substitution at the planning stage can improve the performance of the inventory management system. Moreover, the TSSP method can also be extended to Multi-stage SP (Shapiro et al., 2009).

For unknown environments, the Robust Optimization (RO) technique is used for optimizing the worst-case performance of the SC, where the uncertain parameters may be continuous, varied within a pre-defined interval (the interval uncertainty), or specified with discrete scenarios through the scenario-based method (Pirabán et al, 2019). Gunpinar & Centeno (2016) presented a model for the bloodmobile routing problem, to determine the number of vehicles to deploy each day and minimize the total distance travelled while meeting or exceeding blood demand thresholds. With the RO method, the authors formulated the uncertainty in the number of blood units to be collected on a remote location, within an integer programming approach to model the problem considering variable durations in bloodmobile visits, uncertainty in blood potentials and multiple bloodmobile types. They reached the conclusion that a higher number of bloodmobiles needs to be operated when there is increased demand, but less bloodmobiles are required when there are more donation locations to select from, with shorter distances to be travelled to satisfy the blood demand. Also, when using overstock costs, bloodmobiles end up travelling longer distances to reduce inventory. In addition, the authors also concluded that when deviations from blood potentials are allowed in more donation locations, increasing the capacities of the bloodmobiles may result in an optimal solution with shorter routes.

Regarding fuzzy environments, the Fuzzy Mathematical Programming (FMP) method has been commonly used, in which some constraint violations are allowed. There are 2 types of FMP: flexible programming, that deals with right-hand side uncertainties, and possibilistic programming, that recognizes uncertainties in the objective function coefficients and in the constraint coefficients. For example, to investigate the mobile blood collection system for PLTs production, Rabbani et al. (2017) presented 2 models to cover the bloodmobile collection planning problem, the first using FMP to define the bloodmobiles' locations with the aim of maximizing the amount of collected blood and

minimizing the total operational costs, and the second to cover the shuttles routing problem which was formulated as a vehicle routing problem with time windows.

Furthermore, Simulation can represent in a certain realistic way the system's features and flows of donors, blood products and information throughout the whole SC. Discrete Event Simulation (DES), System Dynamics Simulation (SDS) or Monte Carlo Simulation are methods that can be used to manage uncertainty (Pirabán et al., 2019).

DES is a method of simulating the behavior and performance of a real-life process, facility or system, that is being used increasingly in health-care services. It models the system as a series of 'events' that occur over time, assuming no change in the system between events (Allen et al., 2015). To quantify the impact of a shortened SL of RBCs within a broad and geographically distributed network with multiple supply and demand points, Blake at al. (2013) employed a DES method for the Héma-Québec blood distribution network, in Canada. A series of simulations were conducted under the assumption of a 28-, 21-, or 14-days of SL of RBCs, compared to a base scenario of 42-days of SL, and, for each, the impact on outdates, shortages and emergency ordering frequency was identified under assumptions on the total amount of inventory held and its distribution between suppliers and consumers. The authors concluded that a SL of 18 or 21 days is feasible without excessive increases in outdates, shortage and emergency ordering rates, but reducing the SL to 14 days or lower results in significant challenges for suppliers and hospitals. It was also concluded that holding more inventory increases outdates but results in fewer instances of shortages and emergency orders, and vice-versa for holding less inventory. Also, holding more inventory at the supplier decreases outdate rates, but increases emergency orders from hospitals and, consequently, transportation costs. Another important conclusion from this work was that semifixed collection targets set 6 months in advance may not be compatible with the RBCs' SL of less than 21 days. This simulation study became an appropriate tool for evaluating the systemic impact of shorter SLs for RBCs because it allowed the incorporation of the system's complexities, but since the model was a representation of the Héma-Québec specific system, the results and conclusions obtained are also specific and other systems with different complexities and rules may perform differently, which is one of the disadvantages of using simulation techniques.

SDS is one of the useful techniques to assess the complex behavior of the BSC, firstly defined by Forrester (1994) as a computer-aided approach to analyze and deal with complicated problems by focusing on design and analysis. More recently, Zahraee et al. (2015) applied the SDS method together with the Taguchi method (used to decrease the effects of noise and determine the optimal level of the main controllable factors, so, therefore, to improve the quality of the experiments), in order to design a robust BSC system to improve its efficiency. With their simulation experiments, the noise/problematic factor was the demand, the controllable factors were the arrival rate of donors, the minimum and maximum inventory levels and the blood delivery policy, and the efficiency parameter was the patients' safety. The authors concluded that the arrival rate of donors, the maximum inventory level and the blood delivery policy should be at a high level of 300, 1000 and LIFO, respectively, and that the minimum inventory level should be at a low level of 70, in order to optimize the efficiency of the BSC based on the patients' safety.

Lastly, Monte Carlo Simulation is used to understand the impact of risk and uncertainty in prediction and forecasting models, by modelling the probability of different outcomes in a process that cannot be easily predicted because of random variable interference. Firstly, it takes the uncertain variables and assigns them a random value. Then the model is run and a result is provided. This process repeats again and again while assigning the variable in

question with many different values, until, once the simulation is complete, the results are averaged together to provide an estimate (Kenton, 2021). Simonetti et al. (2014) used this method to model the system dynamics of the United States blood supply with explicit estimation of uncertainty by implementing a stock-and-flow model structure and evaluate the impact on the supply of different policies. The model provided insights on the number of RBC units available in the system at a particular point in time and on which scenario could best approximate the current system. The three independently examined and compared scenarios were the FIFO policy (representing the baseline model scenario), the 'likely oldest' non-FIFO policy (where the older units have a higher probability to be selected) and the 'likely newest' non-FIFO policy (where the newest units have a higher probability to be selected). These scenarios were run independently over a 500 one-year simulation, so with 365x500 iterations per day. The authors estimated that distributing blood under the 'likely oldest' non-FIFO policy and under the 'likely newest' non-FIFO policy corresponded to, respectively, a 6% and 37% reduction on the total supply when compared to the FIFO policy.

Simulation methods are well suited for representing complex stochastic systems. Yet, there is no guarantee of finding an optimal solution. Hence, some recent publications tend to use the combination of simulation and 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 (Osorio et al. (2015) and Pirabán et al. (2019)). In fact, the combination of SDP and simulation was used by Abdulwahab & Wahab (2014) for the establishment of PLTs inventory considering stochastic supply and demand and deterministic lead time, and evaluating three inventory control policies – FIFO, LIFO and Circular (based on reusing or recycling of the products) – in terms of PLTs shortage, outdating, inventory level and reward gained, for the Canadian Blood Service. The authors reached four main conclusions: 1) whenever possible, the blood PLTs bank should be operated close to the optimal inventory level in order to maximize its effectiveness and minimize the number of outdated units and shortages; 2) the lowest number of outdated units and shortage rate are achieved when the O- levels are at about 40%; 3) when the order quantity is received twice a day, the outdated units and shortage drop to about 2%; and 4) FIFO is the best policy to minimize shortages, outdated units and average inventory levels and to maximize the rewards. In addition, FIFO presents the benefit of requiring less computation and implementation times.

Figure 7 summarizes the main modelling techniques used in the literature on the BSC, described previously.

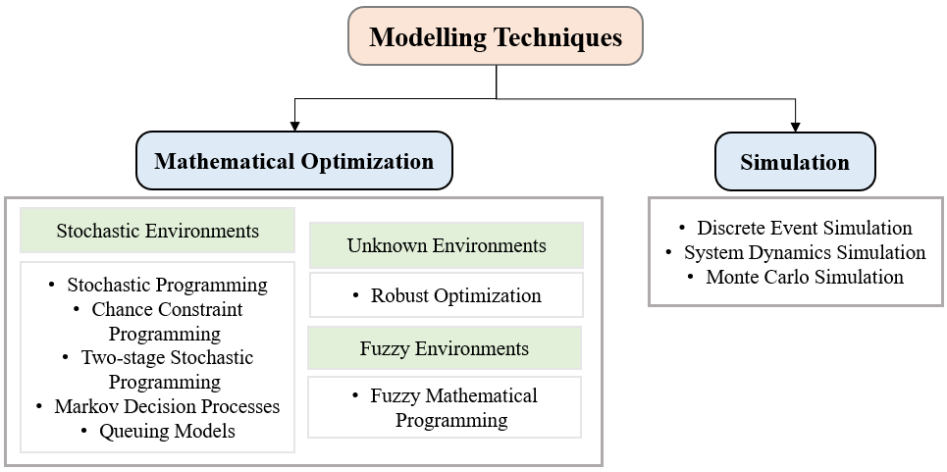

Figure 7 – Main modelling techniques used in the literature to model the BSC, according to Pirabán et al. (2019).

3.7. Main decisions, challenges and objectives

Following what was mentioned throughout the previous sections, it is evident that managing, operating and designing the BSC is a very complex task. Modelling the BSC involves: 1) a complex decision-making process; 2) several constraints, such as the minimum remaining SL of the blood products, the maximum quantity of blood products to transport to DNs or the maximum resources capacity of the facilities; 3) sources of uncertainty, such as supply and demand; and 4) multiple and conflicting objectives, like the minimization of the total costs, wastage and environmental impacts or even the maximization of social impacts.

So, firstly, the management and design of the BSC follows a diverse, challenging and very complex decision-making process. In fact, recently, Torrado & Barbosa-Póvoa (2022) performs a literature review on BSC models, aiming to capture insights into sustainability dimensions in the different BSC studies. From review on several works, including Pirabán et al. (2019), the authors summarize the BSC's main planning decisions identified from the literature, per stage and activity, as illustrated in figure 8.

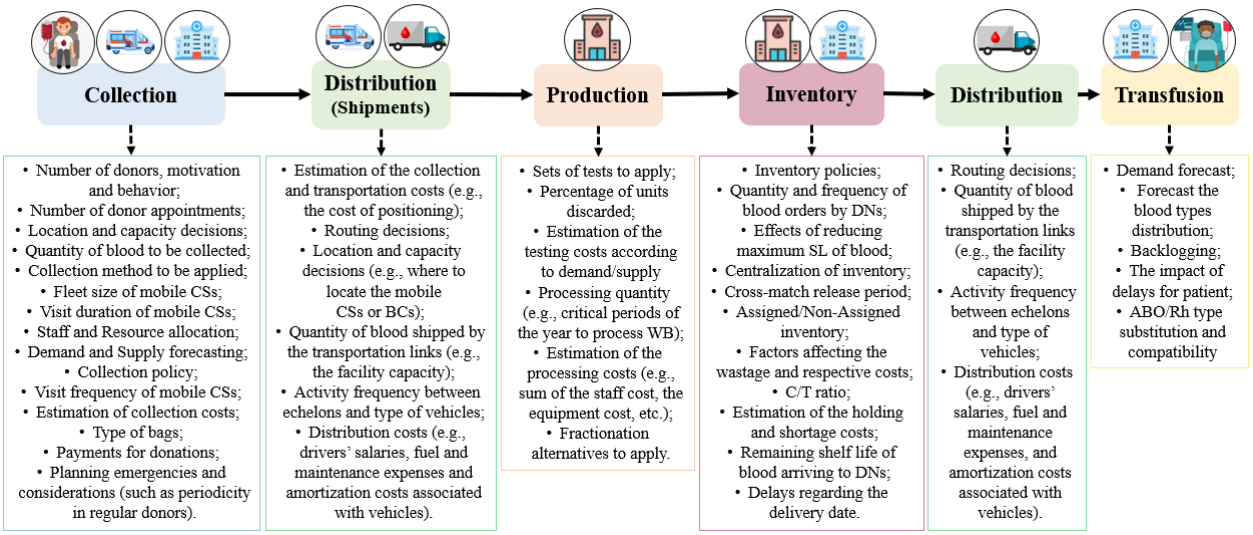

Figure 8 – The main planning decisions of the BSC identified in the literature (adapted from Torrado & Barbosa-Póvoa (2022)).

The decisions mentioned in figure 5 can be distributed along the 3 main hierarchical decision levels. Hence, figure 9, presents the main BSC problems and planning decisions involved, organized by main stage (collection, production, inventory and distribution) and aligned with the main hierarchical decision levels (strategic, tactical and operational), from the reviewing of the works by Torrado & Barbosa-Póvoa (2022), that supports on the review by Osorio et al. (2015) and contributes with additional insights, and Meneses et al. (2022). The latter recently presented a review on the problems of the BSC management according to the planning horizon and developed a conceptual model for each BSC management problem with the main decisions, inputs, parameters, and optimization criteria, for the strategic and tactical planning levels. The main problems, identified by Meneses et al. (2022), are in the colorful boxes, namely network design, collection planning and collection scheduling, production planning and production scheduling, inventory management and demand fullfilment, and distribution planning and transportation scheduling. The bullet points below each colorful box identify the decisions carried by each problem, identified by Torrado &

Barbosa-Póvoa (2022), Meneses et al. (2022) and Pirabán et al. (2019). The strategic level only incorporates one main problem, the network design, focused on determining the BSC configuration with decisions mainly related to the facilities location-allocation and the facilities' capacity, for each stage. The tactical and operational levels incorporate 4 problems, one for each stage. For the tactical level - collection planning, production planning, inventory management and distribution planning – and for the operational level - collection scheduling, production scheduling, demand fullfilment and transportation scheduling.

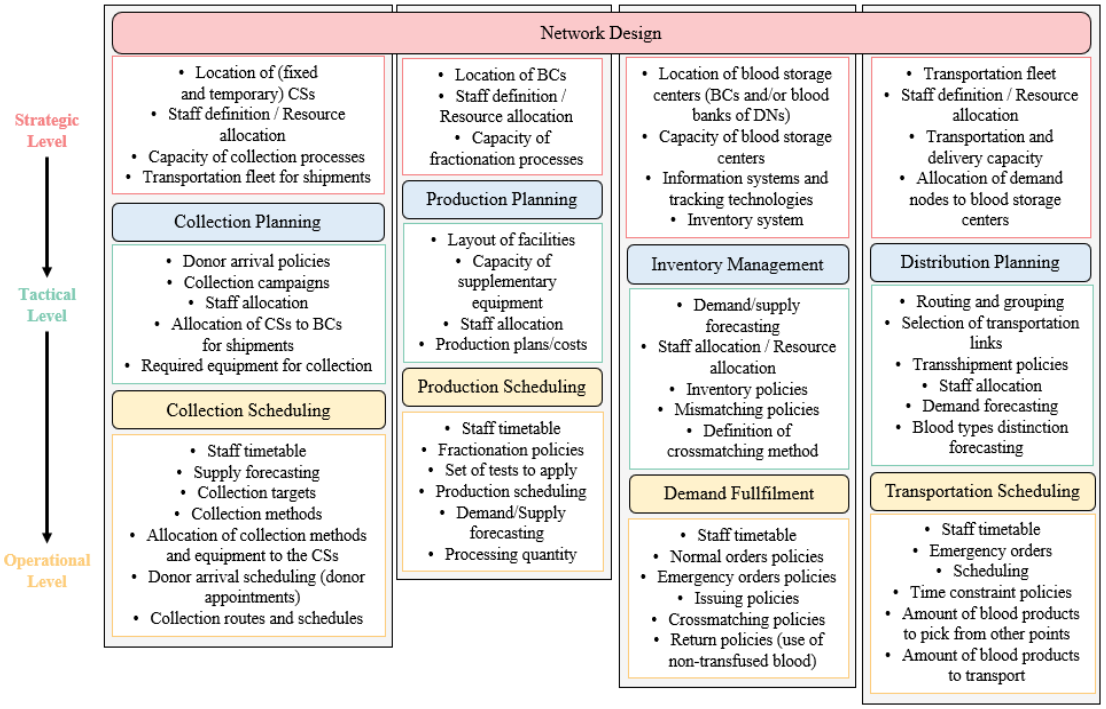

Figure 9 – The BSC main management problems and decisions by stage and hierarchical decision level (adapted from Torrado & Barbosa-Póvoa (2022), Pirabán et al. (2019) and Meneses et al. (2022)).

During the decision-making process several challenges come in the way, which are the constraints faced by the BSC management. In fact, 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 main constraints to model the main BSC planning decisions. The authors identify 3 main clusters of constraints on the strategic level, related to all facilities and stages of the BSC, namely the location, size/capacity and allocation/assignment constraints, with the latter also included in the tactical level. The clusters of constraints included on the tactical level relate to single or multiple stages. The collection and production quantities and timings constraints relate to the collection and production stages only, respectively. The constraints on temporary collection sessions relate only to the collection stage, the ordering policies constraints relate only to the inventory stage and the transshipment constraints relate only to the distribution stage. On the other hand, the inventory fulfillment constraints are related to both the inventory and distribution stages, and the orders' fulfillment constraints along with the resources' capacity constraints relate to all four stages of the BSC. Torrado & Barbosa-Póvoa (2022) also identify the main decisions and constraints from relevant models in published

literature, with emphasis on the strategic-tactical and tactical-operational decision levels. Following this, figure 10 presents the mentioned clusters of constraints by Meneses et al. (2022) with some of the constraints identified by the authors and by Torrado & Barbosa-Póvoa (2022).

It should be noted that this is only a synthesis of key clusters and constraints identified in literature. Besides, this framework only incorporates the strategic and tactical planning levels. However, in fact, some models from literature on this subject have included short term decisions in the same model as long term decisions, which increased the models' complexity and, in turn, reduced their practicability, ending up by failing. So, the right detail for the strategic and tactical planning levels decisions is what should be targeted. Nevertheless, many of the tactical level constraints can be useful for operational problems, where most of the decisions from the tactical level reappear but with a higher level of detail. Hence, decisions such as donor appointments, production scheduling and transportation scheduling are under the operational level, as illustrated in figure 9 (Meneses et al., 2022). In fact, from the 90 reviewed studies by Torrado & Barbosa-Póvoa (2022), 51% of them were dedicated only to the strategic-tactical levels and 49% only to the tactical-operational levels, underlining that the best way to model the BSC is by analyzing the decisions of two consecutive levels together, rather than including strategic with very detailed operational decisions on the same model.

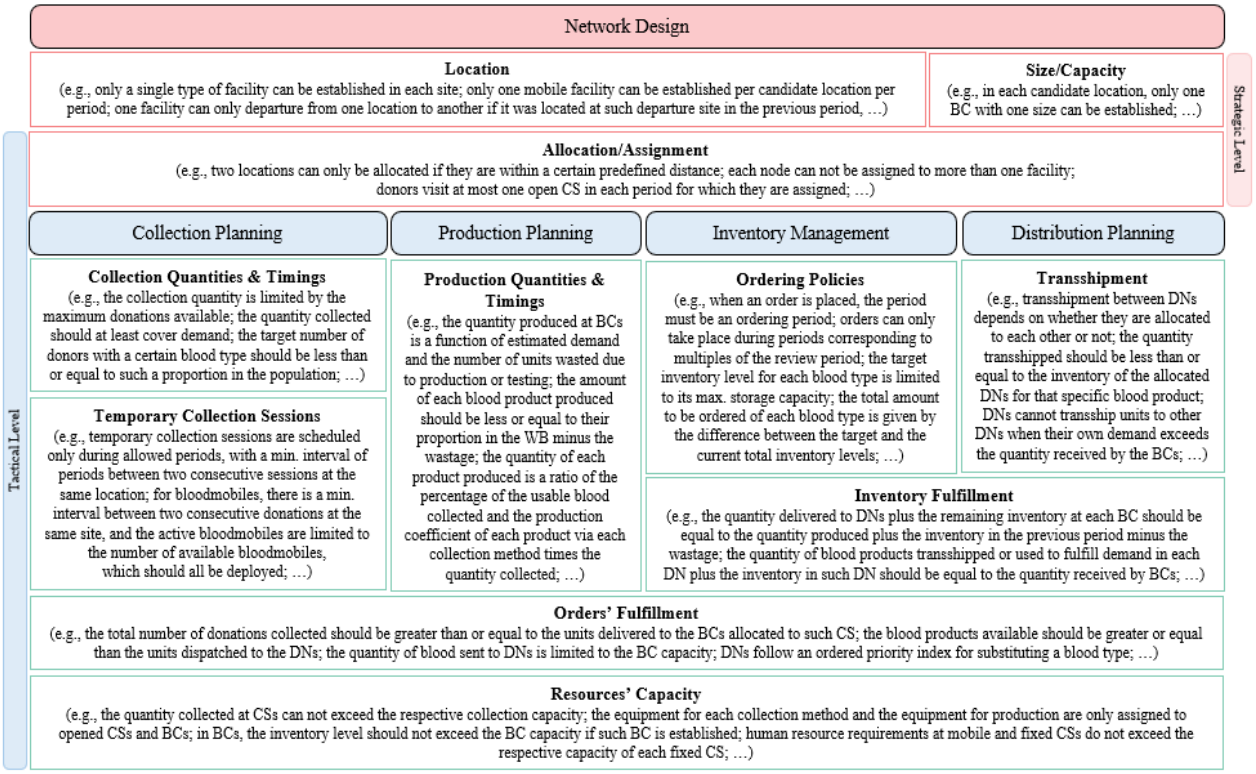

Figure 10 – Strategic and tactical constraints of the BSC management
(based on the reviews by Meneses et al. (2022) and Torrado & Barbosa-Póvoa (2022)).

The BSC is also characterized for its risks and uncertainties, challenging the design and management of the BSC network. Hence, attaining an integrated and well-designed BSC is crucial, especially in unexpected situations, such as medical emergencies that require immediate blood availability. In the BSC, uncertainties are mostly from supply and demand, with risks created from, for example, natural catastrophes or epidemic situations, contributing to additional

uncertainty in supply and demand (Torrado & Barbosa-Póvoa, 2022). 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 optimization criteria identified by both the reviews of Pirabán et al. (2019) and Meneses et al. (2022) identifies various objectives with different relevance. Nevertheless, for both reviews, the most frequent objectives found are the total cost minimization followed by wastage minimization. The total costs mentioned can include the costs of collection, transportation, opening of facilities, processing, inventory, ordering, wastage, shortage and ABO/Rh-/age-substitution. In addition, Torrado & Barbosa-Póvoa (2022) align their research of the BSC with the three sustainability dimensions – Social, Environmental and Economic. According to Purvis et al. (2019), the Social pillar relates to the continued satisfaction of basic human needs of the individuals, the Environmental pillar focuses on the protection of resources, and the Economic pillar measures how corporate abilities use resources to generate sustainable growth. From the 90 reviewed models by Torrado & Barbosa-Póvoa (2022), 47% were focused on the Economic pillar (minimizing total costs), 40% on the Social pillar (maximizing social effects), and only 13% were focused on the Environmental pillar, (minimizing environmental impacts).

3.8. Main chapter conclusions

This chapter presented a literature review on BSC. Firstly, the concepts of SC and SC management and the three main hierarchical decision levels were described. Secondly, the main features of blood were presented, followed by the main literature reviews in the BSC, particularly by Beliën & Forcé (2012), Osorio et al. (2015), Pirabán et al. (2019) and Meneses et al. (2022). Then, the centralized and decentralized network configurations were described. Later, the main stages of the BSC (collection, production, inventory and distribution) were characterized and the main gaps and existent methodologies in literature were enumerated. Finally, the main problems and subsequent decisions, constraints, uncertainties and objectives for modelling the BSC were presented, according to the reviews by Torrado & Barbosa-Póvoa (2022), Meneses et al. (2022) and Pirabán et al. (2019).

Furthermore, the next chapter, on SCs for other perishable products, aims to spot similarities between the characteristics, decisions and problems of other perishable SCs with the BSC, to determine which findings from these SCs can be applied to the BSC to overcome the identified gaps and challenges.

4. Perishable supply chains and perishable supply chain management

This chapter reviews the literature on SC management for other perishable products, in order to find similarities with the BSC. Firstly, section 4.1. details the main characteristics of perishable products and presents some examples. Secondly, section 4.2. explores the main work and reviews on perishable SCs and its management. Subsection 4.2.1. details the AFSC, its main characteristics, decisions and challenges, along with its main modelling constraints, uncertainties and optimization criteria, and subsection 4.2.2. explores possible innovative approaches from the AFSC to apply to the BSC. Section 4.3. concludes this chapter.

4.1. Features of perishable products

In the 1990s, Wee (1993) defined perishability as the decay, damage, spoilage, evaporation, obsolescence, pilferage, loss of utility or loss of marginal value of a commodity that results in decreasing its usefulness. Throughout the following years, perishable products were simply characterized as products with a short lifetime or that easily deteriorate. Recently, Amorim et al. (2013) also presented their own definition of perishability: a good (raw material, intermediate or final 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.

The perishability of products is a tremendous challenge for building sustainable and efficient SCs. The short lifetime of these products not only complicates the inventory management, as they must be processed and moved through the SC to reach the customers before they perish and lose either part or their entire value, but also enforces specific constraints on the different SC processes, such as procurement, production planning or distribution (Duong et al., 2016). Since these products' time span to be consumed after production is limited, extra importance is imposed for the planning of every activity in the SC to ensure that no unnecessary costs associated with wastage are incurred (Araújo, 2018). Besides, the depreciation of the products' value over time reduces the benefits to the society, by reducing revenue, reducing product quality and increasing wastage.

There are 2 types of perishable products: the ones with a fixed SL and the ones with a stochastic SL (Nahmias (1982) and Amorim et al. (2013)). The first relates to products with a well-defined expiry date, beyond which they must be discarded. The utility of these products may decrease during their lifespan, and, if passing it, the products perish completely and become of no value. Examples of these products include food, pharmaceutical and biological products (such as such as vaccines, body organs and, as discussed throughout this work, blood). Hi-tech and electronic products, Christmas items or even high-fashion apparels are also fixed SL perishable products, since they become obsolete after a relatively short period of time due to changing customer expectations, high level of competition, decreased product life cycle or technologic advancements (Chaudhary et al., 2018). Stochastic SL perishable products are those whose lifespan is not predetermined and assumed to be a random variable with a probability distribution that may take on various forms. Their deterioration occurs over time and the products gradually lose their value until they become non-consumable. Examples of stochastic SL perishable products include fresh foods (meats, fruits, vegetables, etc.), bread or flowers (Amorim et al. (2013) and Mirabelli & Solina (2022)).

Thus, perishability affects multiple fields and SCs. The SC of biological products, such as organs or blood transplants, are strongly affected by the perishable nature of the products, as discussed in chapter 3. In the pharmaceutical field, the chemical composition of medicines determines the period of time within which the products are still effective. In the AFSC, often characterized by frequent customer orders of small quantities, tight time windows for deliveries, production and demand uncertainty, the perishability of the products is a challenging point (Mirabelli & Solina, 2022). In subsection 4.2.1., the AFSC is further analyzed, due to its importance and the existence of a more extensive literature search on this topic in comparison to the BSC.

4.2. Perishable supply chain management, a literature review

The first works conducted for perishable SCs date back to the 1970s, with Nahmias & Pierskalla (1973) considering the problem of computing optimal multi-period ordering policies for a product with a fixed SL of 2 periods with random demand, including ordering and holding costs. Later, Hamman (1979) studied the temperature control in the transport and storage of short SL products, concluding that the effect of temperature on milk and milk products highlights possible problems of poor distribution. In the 1980s, Nahmias (1982) studied in-depth ordering policies and inventory management for both fixed and random SL perishable products, considering deterministic and stochastic demand. Then, Pasternack (1985) developed a hierarchical model and used its results for a single period inventory to study possible pricing and return policies, considering decisions faced by a producer of a product with a short SL and demand. The author demonstrated that a policy whereby a manufacturer offers retailers full credit for a partial return of goods may achieve channel coordination, but the optimal return allowance will be a function of retailer demand, meaning that such policy cannot be optimal in a multi-retailer environment. On the other hand, it proved that a pricing and return policy whereby a manufacturer offers retailers partial credit for all unsold goods can achieve channel coordination in a multi-retailer environment. In the next decade, Keilson & Seidmann (1990) analyzed perishable inventory systems under either FIFO or LIFO policies, studying their impact on spoilage rate, mean age at delivery, expected time between stockouts, service level and mean on hand inventory level of the perishable products. The authors concluded that LIFO results in lower age of items delivered and on hand inventories, while FIFO assures a higher service level and longer ties between stockouts. The optimization of the supply rate for both policies also revealed that whenever the sales price is age dependent, FIFO brings higher profits with lower supply rates, and LIFO revealed to be more economical when the utility and sales price of new items is higher than for older items. In addition, this work concluded that under both policies the supply rate must be significantly greater than the demand rate to get a reasonable service level and to account for losses due to the products' perishability. 10 years later, Sarker et al. (2000) developed a model to determine an optimal policy for this type of items under inflation, permissible delay of payment and allowable shortage, to aid retailers in economically stocking the inventory and settle ordering quantities, under the influence of decision criteria, such as time value of money, inflation rates, purchase price of products and deterioration rates. This work showed that the optimal order quantity and maximum allowable shortage vary with the difference between inflation and time discount.

In the 21st century, more research has been developed for perishable SCs and their management. In fact, Mirabelli & Solina (2022) presents a systematic 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. It is important to note that this work only reviews articles with an explicit integration between 2 or more activities of perishable SCs, differing from other reviews that only focus on an individual activity. Amorim et al. (2012) was one of the reviewed articles by Mirabelli & Solina (2022), which, through a multi-objective framework, explores the advantages of integrating the production and distribution intertwined planning problems at an operational level, and formulates 4 approaches where perishable products have fixed and loose SLs: 1) a make-to-order strategy to avoid spoiled products; 2) imposing constraints on the number of periods a products can be in stock; 3) using different holding costs according to the remaining SL of the products; and 4) considering the possibility of attributing a value to the various degrees of freshness when the product is delivered. The authors conclude that the economic benefits derived from using this integrated approach are much dependent on the freshness level of products delivered. Another reviewed article was Neves-Moreira et al. (2019) that tackles a large production-routing problem combining realistic features including multiple vehicles performing routes with time windows, multiple perishable products, and multiple production lines with different specifications. The authors propose a three-phase methodology: 1st) reducing the size of the original problem by simplifying some dimensions, such as the number of products, locations and possible routes; 2nd) constructing an initial solution through a problem decomposition comprising several inventory-routing problems and one lot-sizing problem; 3rd) improving the initial solution by different mixed-integer programming models which focus on small parts of the original problem and search for improvements in the production, inventory management and transportation costs. Through testing this method by a European company's case study, the authors achieve global cost savings when comparing to the company.

From the review by Mirabelli & Solina (2022) it is concluded that, due to its growing importance and relevance, this topic has been considerably studied in literature in recent years. Academic interest in models capable of jointly optimizing production, storage and distribution of perishable products has been growing, not only because of the development of global markets and higher customer expectations that force the maintenance of high levels of performance and market competition, but also because nowadays companies are competing for the reliability and timeliness of the products besides their prices and quality.

4.2.1. The agro-food supply chain

The demand for high quality, value-added and customized agri-food products has been increasing, not only from globalization, but also due to rapid demographic changes and evolving regulatory and legislative interventions. Hence, the design, development and operation of efficient AFSCs that promote sustainability, reduce waste and stimulate healthy sustainable diets, have been increasingly studied and are of great interest in modern management science (Tsolakis et al. (2014) and Agnusdei & Coluccia (2022)). However, AFSCs face many challenges with products' perishability, volatile weather conditions, rapid industrialization of agricultural production, advancements of information and communication technologies (ICTs), complex food quality and safety regulations, changing consumers' lifestyle trends, environmental concerns, arising of new food retailer forms, multiple stakeholders involved, etc. These challenges influence the development of robust and efficient SCs, leading to the adoption of efficient SC management in the agri-food sector (Tsolakis et al., 2014).

An AFSC refers to the production and delivery of agri-products from production to the point of consumption through a series of stages, each adding a specific value to the final product. In fact, the survival and success of the

AFSCs highly depend on delivering fresh products to their customers. Hence, the design of an AFSC plays a crucial role in this regard. So, a general AFSC, as illustrated in figure 11, is characterized by 5 operational echelons (according to a facility-based definition of echelon) – Producers & Farmers, Manufacturers & Processors, Wholesalers, Retailers and Consumers –, supporting product flows, financial flows, information flows and energy and natural resources' flows (Yadav et al. (2022) and Tsolakis et al. (2014)). Following this, an AFSC comprises a set of activities in a "farm-to-fork" sequence including farming (agricultural practices, such as soil preparation, sowing, irrigation and harvesting), production (processing and testing), packaging, warehousing (inventory-related activities), transportation (between echelons), distribution and marketing. Basically, the raw product is harvested, tested and processed (since some agri-food products need to be cut, combined or even cooked), then the final product is packaged and stored at distribution stores to get distributed to various retailers that later sell the product to consumers.

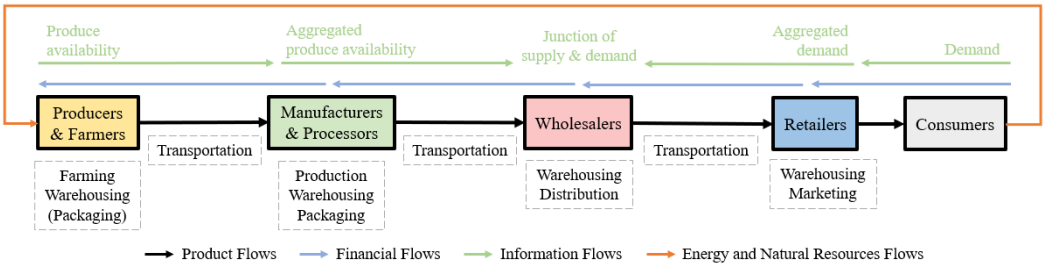

Figure 11 – The AFSC (adapted from Yadav et al. (2022) and Tsolakis et al. (2014)).

These AFSC activities, services and flows are integrated into a dynamic production-supply-consumption cluster, involving various stakeholders (directly or indirectly involved in the SC) with common objectives, such as ensuring food quality, security, safety and sustainability (Agnusdei & Coluccia, 2022). These consist of farmers, producers, intermediaries, manufacturers, processors, transporters, traders, wholesalers, retailers and consumers, as well as research institutions, industries, agricultural cooperatives, non-government organizations or the government (Tsolakis et al. (2014) and Viswanadham & Kameshwaran (2013)). Moreover, each of the mentioned stakeholders has its problems when running their respective activities in the SC. For example, farmers face issues related to the insufficient availability of financial and human resources, fertilizers, pesticides or raw materials, difficulties in marketing and transporting, inadequate consumer prices and infrastructure facilities, and even climate conditions can severely impact the farmers. The intermediaries face complexities such as warehousing management, handling the high perishability of the agri-products or lack of consistency between supply and demand. The consumers also face challenges such as safety and quality issues or fluctuations in the agri-products prices (Yadav et al., 2022).

Just like for the BSCs, the AFSCs also exhibit unique and specific characteristics that raise the need for special managerial capabilities. Agri-products are characterized by their uniqueness, heterogeneity and perishability. In fact, the products can be crop-based or animal-based. The crop-based ones can be subdivided into highly perishable products, such as fruits and vegetables, and slightly perishable products, such as cereals or nuts (Ahumada & Villalobos, 2009). Hence, AFSCs have specific requirements for transportation, storage conditions, quality and material recycling, imposed by end customers, by food safety and public health regulations and directives, or even by national/international legislations and the government. The seasonality in harvesting and production operations and the variability of quality and quantity on farm inputs and processing yields also characterize the agri-products and the

AFSCs, along with environmental issues, such as carbon and water footprints (Van der Vorst (2000, 2006) and Esteso et al. (2018)). It is also important to note that food quality is measured by the products' characteristics, such as taste and texture, and the customers' perceptions of them, whereas food safety is measured as a binary variable determining if the products are allowed for consumption or not (Akkerman et al., 2010).

Following this, the unique and specific characteristics of the AFSCs make designing, managing and operating them a complex and integrated decision-making process. In fact, 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. This review is restricted to the conceptual framework that deals with the strategic decision of configurating the SC network, within the hierarchical decision framework for AFSC management proposed by Tsolakis et al. (2014). Firstly, Esteso et al. (2018) propose 7 strategic decisions for designing the SC: Facility Role (defining the processes to be performed at each facility and/or the facility type to be opened at each location), Facility Location (deciding where to locate a facility), Capacity Allocation (defining the capacity to allocate each facility), Maintain/Close Facility (deciding as to whether close or keep open locations over the horizon), Supply Allocation (selecting which suppliers will provide each processor), Facilities Allocation (defining the connections among AFSC's nodes) and Market Allocation (selecting which facilities will serve each retailer or end customer). Then, the authors identify 9 tactical and operational decisions, exposed while designing the network, mentioned as the planning decisions - Energy Type (selecting the energy source to be used in each AFSC process), Inventory (defining the products' quantities to store per facility and time period), Laboring (defining the number of laborers needed at each facility), Procurement (defining the amount of raw materials or products to buy from suppliers), Production (defining the number of products to be manufactured in each production plant), Routing (defining the routes to follow during product distribution), Transported Quantity (defining the quantity of products to be transported between locations), Transport Mode (selecting the transport mode to be used for each delivery) and Transport Capacity (allocating the transport capacity). Time horizon decisions are also proposed by the authors, since an AFSC can be designed by considering a single time period or multiple time periods, depending on the addressed decisions. The designing and planning decisions proposed by Esteso et al. (2018) are enumerated in figure 12. In addition, the authors propose a conceptual framework for reviewing existing AFSC design models and determine if such characteristics have been addressed, to identify possible gaps and validate the proposed framework.

As mentioned previously, the reviewed conceptual framework by Esteso et al. (2018) is restricted to the work of Tsolakis et al. (2014). The latter made a synthesis of all the decisions identified for their on-going research, recognizing the natural hierarchy of the decision-making process for the design and planning of AFSCs, that, in general, tackle issues related to crops planning, harvesting practices, food processing operations, marketing channels, logistics activities, vertical integration and horizontal co-operation, risk and environmental management, food safety and sustainability assurance. Thus, Tsolakis et al. (2014) provide a taxonomy of existing efforts in the reviewed literature up to 2014, mapped on the main hierarchical decision levels – strategic and tactical & operational decisions – which are also enumerated in figure 12 besides the ones by Esteso et al. (2018). The first included Farming Technologies (determining requirements and expenditures for farming machinery and applications, cooperative schemes for their utilization, etc.), Sustainability Ensurance (adopting Corporate Social Responsability (CSR) business practices, waste management policies, CO_2 and water footprints control systems, green farming practices, etc.), Partnering

Relationships (determining partners' roles, integrations, collaborations and contract types), Investment Portfolio (selecting financing options and investments for resources and infrastructures) and Quality & Performance Management (selecting quality management policies, Key Performance Indicators (KPIs), data handling mechanisms, measuring methods, etc.). Tactical & operational decisions included Farming Operations (selecting and scheduling the types of planting and harvesting operations), Packaging (defining the packaging techniques and conditions) and Food Safety (adopting tracking and tracing technologies to ensure food safety throughout the entire SC).

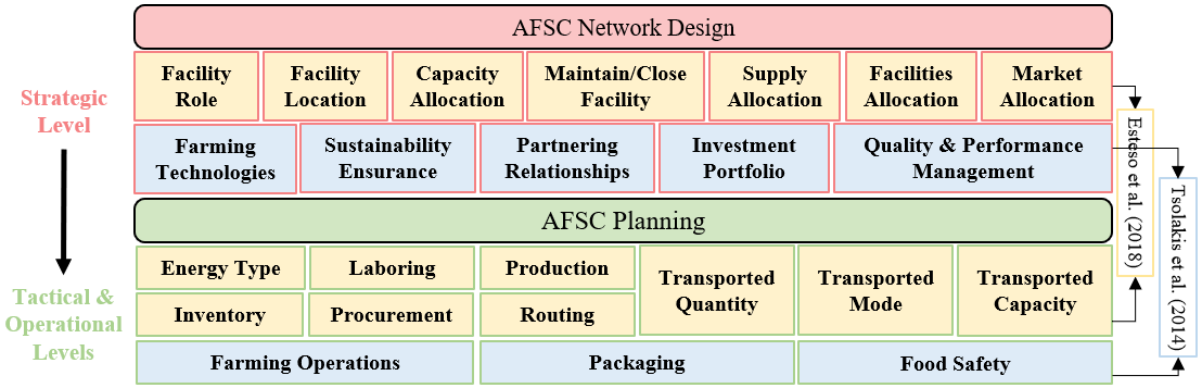

Figure 12 – The AFSC management decisions by hierarchical decision level (based on the reviews by Esteso et al. (2018) and Tsolakis et al. (2014)).

During the decision-making process represented in figure 12, for the designing and planning of the AFSC, 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. That said, the constraints proposed by Esteso et al. (2018) for the AFSC, presented and detailed in figure 13, relate to Supply, Capacity, Number of Locations, Distance, Budget, Product Flow, Time, Service level, Production, Routes and Perishability. Additionally, Sustainability should also be added to this list of constraints, as it is of great importance for the SC, since, for example, CO_2 emissions or water consumptions should be constrained to their minimum.

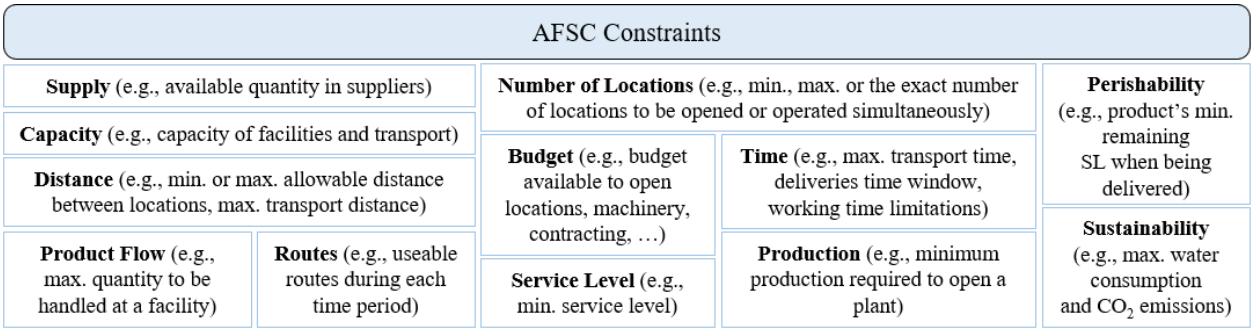

Figure 13 – The AFSC constraints (based on the review by Esteso et al. (2018)).

As for the uncertain parameters in the AFSC proposed by Esteso et al. (2018), these are presented and detailed in figure 14, and relate to the Products, the Processes, the Market and the Environment.

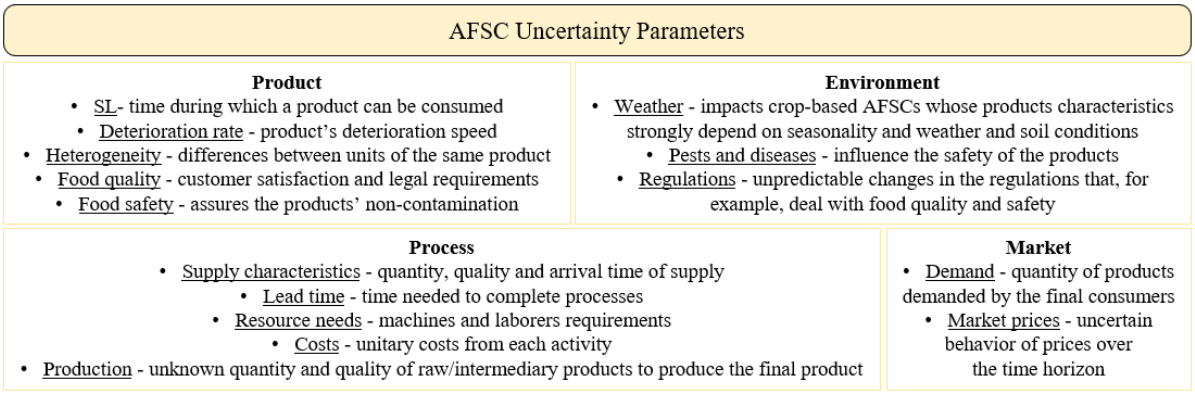

Figure 14 – The AFSC uncertainty parameters (based on the review by Esteso et al. (2018)).

AFSCs main management challenges were also identified in more recent reviews, such as Yadav et al. (2022). Yadav et al. (2022) present a systematic review of 108 articles on AFSCs, identifying their current status and various challenges and reviewing the research contribution in the field of designing agri-food SC network, while also investigating and measuring the performance of the AFSC through performance indicators. The authors divide the AFSC management challenges into four categories: Sustainability, Food Waste, Food Safety & Security and Miscellaneous. In addition to the constraints and uncertainties presented in figures 13 and 14, more challenging features of the AFSC management from these two previously mentioned reviews are highlighted by Tsolakis et el. (2014), such as: legal and political issues, limited collaborations, modernization of AFSCs (demanding additional technical and managerial capabilities), pressure from government regulators, non-governmental organizations or global competition, weak environmental enforcement and regulation (lack of awareness between stakeholders and low CSR implications), high number of intermediaries, lack of coordination, information gaps between stakeholders and their product expectations, food fraud and corruption, or even poverty and lack of reachability to remote areas.

Regarding the optimization criteria mentioned 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. Farahani et al. (2014) defines a SC as 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. So, to optimize the AFSC performance and generate a positive impact on sustainability, models should pursue multiple objectives related to the three mentioned aspects: economic (such as maximizing profits or minimizing costs), environmental (such as minimizing CO_2 emissions, water and energy use and wastage levels) and social (such as maximizing employment creation and customer satisfaction or minimizing delivery times). However, according to Esteso et al. (2018), most models design Lean SCs, while Green and Sustainable SCs are less considered. All models pursue economic objectives, considering the minimization of costs or maximizing the profits. Social objectives are less pursued, for minimizing total delivery times, maximizing customer satisfaction (also measured as demand fulfilment), maximizing product quality, job creation and the conditional value-at-risk of customer services. Minimizing waste and other environmental objectives, such as CO_2 emissions and water usage, are even less addressed objectives. Paam et al. (2016) also shares these conclusions in their assessment of the studies in the field of agri-business planning models. Their review, besides showing that most have a single objective

function, also reveals the orientation towards the main objective of minimizing costs or maximizing profit, instead of minimizing food loss and wastage levels. It is important to refer that the most widely costs are related to the location of facilities, production and transportation, being the transportation costs mentioned in all reviewed models by Esteso et al. (2018). Other costs can include inventory, procurement, product waste, unmet demand, closing locations, energy use or laboring costs. Table 10 enumerates the AFSC optimization criteria, or main objectives, found in the review by Esteso et al. (2018), top-down from the most to the least frequently addressed.

Table 10 - Optimization criteria in the AFSC, according to the review from Esteso et al. (2018).

Measure	
Economic objectives	Min. Total costs
	Max. Profit
Social objectives	Min. Total delivery times
	Max. Customer satisfaction
	Max. Product quality
Environmental objectives	Min. CO_2 emissions
	Min. Water usage

4.3. Agro-food supply chain insights to apply to the blood supply chain

Given what was described for the AFSC, it is clear that the AFSC is very similar to the BSC, namely when it comes to the products' characteristics. Firstly, both agro-products and blood products are irreplaceable. There are no substitutes for blood, as there are no substitutes for fresh foods, only artificial and non-fresh products. Heterogeneity is also a common characteristics of both products. Agro-products subdivide into different types of products, which can have different shapes, textures or flavors that differentiate them from others. The same happens for blood, as WB can be fractionated into RBCs, PLTs, Plasma or Cryo, and there are eight blood types, according to the ABO/Rh system, that differentiate them from each other with specific compatibilities. Yet, 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. The perishabilities of the products are not exactly the same, but they are very close, making them comparable. In fact, if comparing with crop-based products, most fruits have a smaller SL then WB and RBCs, which are the most used blood products for transfusion according to the Portuguese case, as mentioned in section 2. For example, melons refrigerated at (0-4,4)ºC and mangoes refrigerated at 12ºC have a SL of 2 or 3 weeks, whereas WB and RBCs, refrigerated at each specific temperatures mentioned at table 2, have SLs of 3 to 7 weeks or 6 weeks, respectively. Some vegetables also have a smaller SL, such as asparagus, courgettis and green beans. However, other vegetables have SLs of several months, namely carrots and dry onions refrigerated at 0ºC or sweet potatoes refrigerated at (12-16)ºC (Liberty et al., 2013). As for cereal grains, these are considered slightly perishable products, with greater SLs. For example, wheat, dry corn and oats, refrigerated at 0ºC, can hold up to 1 or 2 years, and at room temperature, such as when stored in a pantry, from several months or even 1 year (Donaldson, 2016).

Consequently, the decision-making process for the AFSC (illustrated in figure 12) can be adapted to the BSC. Regarding the strategic level, decisions related to the facilities – Facility Role, Facility Location, Facilities Allocation

and Maintain/Close Facility – are also important in BSC management, specifically for CSs and BCs. Allocation decisions are also present in the BSC, for Capacity (at CSs, BCs, DNs and transportation), Supply (on selecting which CSs will provide each BC) and Market (on selecting which BC will serve which DNs). The remaining strategic level decisions are more directed to the AFSC but can also be adaptable to the BSC. For example, deciding on Farming Technologies in the AFSC can be comparable with deciding on the blood collection methods for the BSC, determining which method will be used in each CS, considering the different equipment's requirements, staff, types of obtained products, etc., although at the BSC this is more linked to the tactical and operational levels. As for Ensuring Sustainability, it is important to prevent blood wastage and outdated units, CO_2 emissions and energy consumption from the BSC processes, etc. Lastly, decisions on Partnering Relationships, Investment Portfolio and Quality and Performance Management are also comparable to the BSC. For example, the first for blood transportation vehicles, such as for the Portuguese case, since IPST does not own transportation vehicles for plasma, so external contracting needs to be assured, the second for the opening of CSs or collection equipment, which depends on initial investments, and the third on ensuring the safety and flow of the blood products along the BSC. Regarding the tactical & operational levels, most decisions are adaptable to the BSC, although the one on Energy Type is more suitable for AFSC processes rather than for the BSC, unless when it comes to the blood transportation process, selecting the energy used by the vehicles, which is very conditioned by the existent and available fleet. Decisions on Laboring, Production, Procurement and Inventory are also suitable for the BSC. Laboring relates to the personnel and staff needed for performing the BSC processes, Production to the quantities of RBCs, PLTs, Plasma or Cryo to produce at the BCs, Procurement for the collection of blood and defining the quantity of products to collect from donors, and Inventory for defining the quantity of blood products to store at the BCs and the blood banks of the DNs. Decisions on transportation and routing are also suitable for the BSC. However, Transport Capacity and Transport Mode are included at the strategic level in the BSC decision-making process rather than at the lower levels. Lastly, Farming Operations, Packaging and Food Safety decisions are also comparable to the BSC, the first by deciding on the collection methods, the second on the bagging of blood products after collection or production and the latter on blood safety.

So, given the similarities between the AFSC and the BSC decision-making processes, it is clear that the AFSC constraints (identified in figure 13) are all applicable to the BSC, regarding blood products and blood-related processes and activities. As for the SC's uncertainties, the 4 clusters of uncertain parameters presented at figure 14 are obviously directed to the AFSC, but some can be comparable with the BSC uncertainties. From the Product cluster, the BSC carries the same uncertainties, although the heterogeneity of blood products is only an uncertainty before testing in case the donors' blood type is not known a priori, and the product's quality also depends on the results of the tests applied on the donations. The Process and Market clusters are also adaptable for the BSC, but the Environmental cluster is not that relevant, unless for the cases when diseases influence the eligibility of the donors and changes in the safety regulations, for example for the required tests to apply on the donated blood, condition the supply of blood. Pests are not at all comparable to the blood's case, but the weather can in a certain way influence the donations by conditioning the donors to attend CSs. Lastly, regarding the optimization criteria, the models for the AFSC and for the BSC have very similar objectives. The minimization of total costs is usually the main goal for both SCs, and both SCs target objectives from the three main sustainability pillars - economic, social and environmental objectives. Therefore, some methods from the AFSC can be applied and explored for the BSC. The most relevant models identified from

Esteso et al. (2018), that is, the ones with the more knowledge transfer potential, were Amorim et al. (2016), Govindan et al. (2014), Allaoui et al. (2018) and Singh et al. (2018), in order to find possible transfers of knowledge to the BSC.

Starting with Amorim et al. (2016), this work presents a new 2-stage stochastic mixed-integer programming model for the supplier selection that maximizes profit and minimizes risk of low customer service, considering some of the main complexities of food SC management, particularly the perishability of both raw materials and final products, the uncertainty at both downstream and upstream parameters (suppliers' raw material availability, lead time, spot market prices, demand, etc.) and age dependent demand. So, firstly, it is decided the branding and quantities of products to be procured in advance from each supplier, and then, in the second stage of the model, the produced, transported and procured quantities of the products are decided. Hence, the authors assess the relevance of including tactical production and distribution planning in the supplier selection decision. In fact, one of the main conclusions is that the integrated approach of both the strategic and tactical levels is advantageous to make better decisions on the sourcing of perishable raw materials for the production of final products, since the advantages of the premium price that customers are willing to pay is undervalued by decoupled approaches. The main reason Amorim et al. (2016) was chosen to be studied for possible transfers of knowledge is that it focuses on the agro-food products' remaining SL after production and the age of each stored product, which are important features of the blood products, usually addressed in BSC models. Besides, this model also takes into consideration the food quality and heterogeneity of products, which are other similar features to blood products. In this model, the design decisions lean on the Supply, Facility and Market Allocations, and the tactical & operational decisions lean on the Inventory, Procurement, Production and Transported Quantities (as illustrated in figure 12), and the constraints used in this model are mostly included in the Supply, Capacity, Production, Product Flow and Perishability clusters (as illustrated in figure 13). Some constraints used by Amorim et al. (2016) can be interesting innovations to apply to a BSC model, such as the ones forcing the utilization of local raw materials for products branded as local, which, according to the reviewed literature for this dissertation, are not very addressed in BSC models. However, other constraints, such as for inventory balance and update of the stock of the raw materials and final products, are not innovative for the BSC, as most BSC models already consider the same set of constraints, particularly the Capacity, Product Flow and Perishability constraints.

A routing model by Govindan et al. (2014) was also studied, which introduces a 2-echelon location and routing problem with time-windows for sustainable SC design. Decisions include the number and location of the facilities, the size of shipments and the most efficient routes to optimize the amount of products delivered to lower stages and routes at each level, with the goal to minimize the total costs and environmental effects throughout the AFSC. This model takes into account the products' perishability, but only considers 1 type of product and ignores important uncertain parameters. Also, for being a routing problem, the decisions, constraints and costs contemplated in this model are in the operational decision level, focusing more on the Routes and Time constraints clusters (figure 13). So, although included in the operational decision level, the consideration of time window violation penalty costs is an interesting and innovative finding from this AFSC model to possibly by applied to the BSC. However, again, most of this model's constraints, from the Routes, Number of Locations, Time and Capacity clusters, are already used in BSC models.

As for Allaoui et al. (2018), the authors also propose an innovative 2-stage hybrid solution methodology, firstly to select the potential partners (suppliers, transformer sites, and distributor sites) using multicriteria decision making, and secondly to develop a multi-objective mathematical model to optimize the design of the SC. So, the potential

partners are evaluated with a certain set of criteria that determines their efficiency score with respect to their performance in the SC, and if the number of partners is too large, a filter process is activated and only the sites with the best performance scores are selected for the second stage of the model. Also, this model simultaneously takes into account all 3 dimensions of sustainability, being an innovative approach when it comes to considering water footprint, CO_2 footprint and the number of jobs created, along with economic cost in terms of multi-objective optimization for designing sustainable 4 echelons SCs. This 2-stage methodology and the account for the three sustainability pillars are possible innovations to consider for the BSC. However, most of the mentioned constraints in this model, included in the Supply, Capacity and Routes clusters of constraints, are already considered in BSC models.

Finally, Singh et al. (2018) proposed a mathematical programming model, which includes interesting features to apply to a BSC model. It is a cold chain location-allocation configuration decision model for the shippers and customers, with the goal to identify the locations of the SC sites on the basis of customer requirements to meet the perishable products' demands, as well as to minimize total costs, including transportation, energy and unmet demand costs. Besides taking into account the perishability of the products, this model also addresses the deterioration of the products' value with respect to time or before the expiry date, along with other important factors to consider in cold chains, such as the coordination among fragmented and heterogenous customers, opportunity cost in terms of deterioration of value with time, units of product transportation and distance calculation. Most of this model's constraints and parameters are similar to what is used in the BSC. However, it includes a new parameter never applied to the BSC, at least not in the authors knowledge, that the authors called the Service Distance Requirement (SDR), dependent on the Expected SL (ESL) for each retailer. Basically, in the considered AFSC by Singh et al. (2018), each retailer manages products that are in a certain stage of the products' life cycle, the ESL, and the same product might be required by different retailers with different ESLs. This can be potentially very advantageous for avoiding wastage since a product reaching its ESL in a retailer can still be potentially used by another retailer before reaching its expiry date. The SDR is calculated taking into account the expiry date and the ESL of the products and the average speed of the distribution vehicles, and it is compared with the actual distance between retailers. Hence, the products are only distributed in case the actual travel distance is less or equal to the respective SDR, to ensure that the products reach the retailer with the respective ESL and before reaching their expiry date. This is a very interesting and innovative approach to apply to the BSC model.

After analyzing the models reviewed by Esteso et al. (2018), additional research was made to find more innovations to apply to the BSC, particularly leaned on cold chains, which, is a feature not often considered in BSC models. Qi & Hu (2020), although focused on the operational level, proposes a mathematical optimization model for the vehicle routing problem for emergency cold chain logistics, with the goal to minimize loss and wastage of agro-products during distribution, and to minimize the costs of cargo damage, fuel consumption and refrigeration cost. Thus, the authors present the parameters that describe these costs, which are interesting features to apply to the BSC.

- **Innovations to be used for the BSC**

As described previously, Singh et al. (2018) and Qi & Hu (2020) presented interesting insights from the AFSC that can be applied to the BSC. Hence, these are the innovations considered for the BSC. The first proposed the concept of the retailers' ESL for the agro-products. Basically, this means that the different retailers have different requests for

the age of the products that they sell and store. A certain retailer can sell and store products until reaching their SL, but others only sell and store products until a certain age, the ESL, before their expiry date. For the BSC, that can be compared to considering the maximum age that the DNs request and use the blood products, since DNs can also differ from each other by having specific demands for blood products with specific ages. This maximum age of blood products stored and used in a DN, besides being the maximum point for the requested blood units to the BC, can also be the returning point of old blood units to the BC. Thus, the first innovation to incorporate in this dissertation model is inspired by Singh et al. (2018), and it is the reutilization of blood products between DNs, using the particular maximum age for each blood product and DN, with the goal to minimize wastage of blood units. The DNs order blood products with a certain maximum age. In case the blood in the inventory of the DNs reaches that respective maximum age, then it is time for the DNs to return those units to the BC. Since the maximum age for blood products differs from DN to DN, these returned orders by a DN can still have the chance to still be reused by another DN before reaching the product's expiry date in the BC, in case the products are still fitted for the demand of that DN. Singh et al. (2018) also proposed the SDR, taking into account the ESL, the SL of the products and the average speed of the vehicles. This parameter is compared to the actual distance to be travelled, in order to know if the products reach their destination still with the respective ESL and before reaching their expiry date. This is the second innovation to incorporate to the BSC model, to know whether the redistributed blood arrives at the target DN before reaching the respective maximum age and become unfit for meeting demand at the DN. Finally, Qi & Hu (2020) proposed interesting ways to calculate refrigeration and fuel costs, during transportation, which are innovative cold chain parameters to include in the model since they are not very common to be considered in BSC models. The incorporation of the previously mentioned innovations is what is going to be explored in this work's model, mainly in order to understand if it is optimal for reducing wastage of blood units in the BSC, which is one of the most concerning problems in the BSC.

4.4. Main chapter conclusions

This chapter gives insights on SCs for other perishable products besides blood. Firstly, the unique features of perishable products are presented, which consequently become a tremendous challenge for building sustainable and efficient SCs. Then, the main reviews on perishable SCs were explored, with Mirabelli & Solina (2022) presenting one of the most recent systematic literature reviews on the integrated management of perishable SCs, concluding that the importance and relevance of this topic has been constantly growing over the recent years. Finally, the AFSC is more extensively explored due to the existence of a more extensive literature search on agro-food and to its similarities to BSC. The AFSC management, main characteristics, stages, problems, decisions, constraints, uncertainties and objectives are presented, mostly based on Esteso et al. (2018). Following this, at the end of this chapter, innovative approaches reviewed from AFSC management literature are presented, with the goal to find possible transfers of knowledge from the AFSC to the BSC.

In fact, the BSC and the AFSC are similar in the way that both carry real-world challenges, such as the perishability of products, product safety and quality requirements, environmental concerns and even changing trends in supply and demand. Moreover, both SCs have similar decisions, problems and objectives. Hence, the knowledge acquired from studying the AFSC, particularly from Singh et al. (2018) and Qi & Hu (2020), can be applied to the BSC in order to build an innovative BSC model, as described next in chapter 5.

5. Problem definition and model formulation

This chapter follows what was contextualized and theoretically explained in the previous chapters, where the necessary insights for the development of the proposed optimization model for this work were presented. Firstly, section 5.1. defines the problem to be managed and all the raised assumptions. Then, section 5.2. presents the proposed mathematical formulation of the model, with all the sets, parameters, variables, constraints, calculations and the objective function. At the end, section 5.3. concludes this chapter.

5.1. Problem definition

This model is mainly supported in the main innovative transfer from the AFSC, by Singh et al. (2018). 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. Also, 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 redistribution of blood, and increasing the quality of transfusions, through the introduction of a maximum age of transfusions at each DN. The model focuses on 2 blood activities around 2 main blood facilities – inventory management, at both the BC and the DNs, and (re)distribution, from the BC to the DNs and vice-versa. Hence, it is not restricted to a single echelon as it considers more than one type facility (1 BC and multiple DNs) and more than 1 stage. Figure 15 shows the conceptual model of this work.

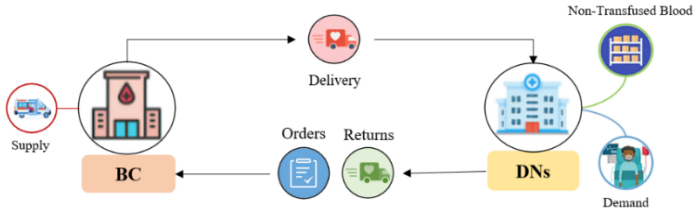

Figure 15 – Conceptual model.

(Re)Distribution:

- At the first time period, there are no (re)distributions, only transfusions at the DNs. (Re)Distribution only happens for the first time at the second time period, according to the ordered quantities by the DNs at the end of the first time period.
- Blood units are sent to the DNs from the BC at the start of each time period (except the first one), according to the FIFO policy, the ordered quantities by the DNs, the DNs' maximum ages of blood products and the units' Service Distance Requirements, the last two being innovative transfers from the AFSC, by Singh et al. (2018).
- 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. These are calculated according to the transfer from the AFSC, by Qi & Hu (2020).

Inventory management, at the BC:

- The BC is initially empty, with no units in inventory. Thus, there is no waste at the first time period, at the BC.
- The inventory levels of the BC depend on the daily supply of fresh units from collection and production, on the (re)distributed units to the DNs and on the returned non-fresh 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 for the BC.
- 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 first 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, the inventory of the DNs is again updated.
- 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 the orders for the next period.
- Final inventory update: according to the discarded units, the inventory is updated.
- 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.

Therefore, in summary of what was explained above and as will be further outlined in section 5.2., the formulated model acts as illustrated in figure 16: it is given its initial parameters, from which it obtains various results in respect to its main objective, to then draw the intended conclusions.

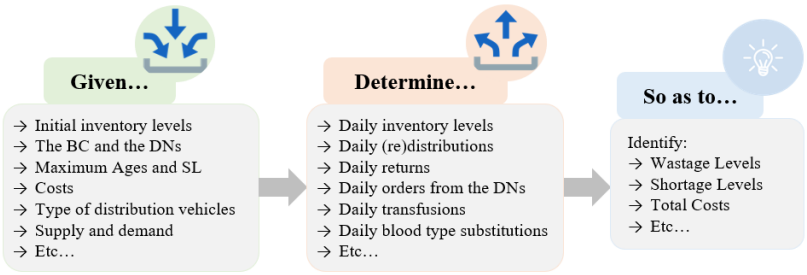

Figure 16 – The functioning and purpose of the model.

5.2. Model formulation

The model presented in this section follows what was mentioned previously and represented in figures 15 and 16. Although incorporating insights from the AFSC, it mainly considers important characteristics from the BSC described in chapter 3, particularly the uncertainty in supply and demand, the ABO/Rh compatibility and the substitutability between blood types. Subsection 5.2.1. presents the model notation, which includes the sets and indices, the decision variables and, lastly, the parameters used as input data and auxiliar decision expressions. Subsection 5.2.2. presents all the model's constraints and calculations, and, finally, subsection 5.2.3. presents the objective function. However, firstly the model is formulated as a Mixed Integer Non-Linear Programming (MINLP) model. Given the complexity of solving models of this nature, the non-linear constraints are then reformulated in order to transform the model into a Mixed Integer Linear Programming (MILP) model. Hence, a linearized version of the MINLP is presented at subsection 5.2.4.

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 $p1$ for transfusions at the DNs (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 blood 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 blood type $p2$ (from collection and production) 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 blood type p2, at the BC and the DNs.

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

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

$DemQt^{t}_{d,p1,p2}$ Demanded quantity of blood product $p1$ of blood 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 blood type $p2$ with age a, at DN d, before meeting patients' demands.

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

$$MComp_{p2,p2'} = \begin{bmatrix} 0 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad MSubs_{p2,p2'} = \begin{bmatrix} 0 & 1/7 & 1/6 & 1/5 & 1/7 & 1/5 & 1/5 & 1 \\ 0 & 0 & 0 & 1/6 & 0 & 1/6 & 0 & 1/2 \\ 0 & 0 & 0 & 1/7 & 0 & 0 & 1/6 & 1/3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1/4 \\ 0 & 0 & 0 & 0 & 0 & 1/7 & 1/7 & 1/5 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1/6 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1/7 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad p2, p2' \in P2$$

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

$SS_{d,p1,p2}$ Minimum inventory (safety stock), at DN d, for blood product $p1$ of blood 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 blood 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 blood type $p2$ with age a, at time period t, after meeting patients' demands.

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

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

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

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

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

$OrdQt_{d,p1,p2}^{t}$ 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.

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

$RefriUn_{d}^{t}$ Refrigeration cost of unloading blood units at DN d, at time period $t \geq 1$.

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

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

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

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

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

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

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

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

- **Decision variables**

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

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

$inv_{d,p1,p2,a}^{t}$ 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.

$inv_{p1,p2,a}^{t}$ Integer variable for the inventory level of blood product $p1$ of blood 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 blood 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 blood 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 blood 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 blood 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 blood 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 blood 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 blood 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 the ordered quantities of blood product $p1$ of blood type $p2$, from DN d, 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 blood type $p2$ with age a, at time period t.

In short, figure 17 illustrates how the previously described decision variables relate with the BSC stages and facilities considered in the formulated model.

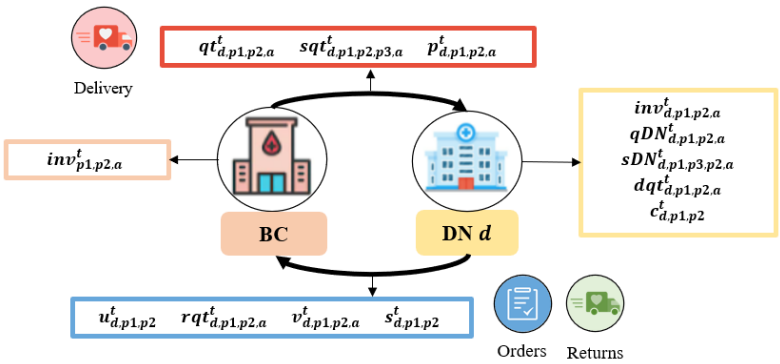

Figure 17 – The decision variables and their relationship with the BSC model's stages and facilities.

5.2.2. Constraints

Initial inventory update, at the BC: for each blood product, blood type and age, each period's inventory is established by the new fresh quantities from production (for 0 days of age) or by the sum of the respective inventory from the previous period and the quantities returned to the BC from the DN minus the quantities redistributed to the DNs (for ages between 1 day and the SL).

$$inv^{t}_{p1,p2,0} = CPQt^{t}_{p1,p2}, \qquad \forall\, t, \forall\, p1, \forall\, p2 \tag{1}$$

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

Wasted quantities, at the BC: each period's wasted units equal the inventory older than the SL.

$$WQt^{t}_{p1,p2} = \sum_{a \geq SL_{p1}} inv^{t-1}_{p1,p2,a}, \qquad \forall\, t \geq 1, \forall\, p1, \forall\, p2 \tag{3}$$

Total inventory update, at the BC: for each blood product and blood type, each period's inventory is the sum of the respective inventory for all ages below the SL.

$$Inv^{t}_{p1,p2} = \sum_{a=0}^{SL_{p1}} inv^{t}_{p1,p2,a}, \qquad \forall\, t, \forall\, p1, \forall\, p2 \tag{4}$$

Available inventory for (re)distribution to the DNs: each period's quantity of each blood product and blood type from the BC to be redistributed to the DNs is restricted to the available inventory of the BC with ages below the DNs' respective maximum ages.

$$qt^{t}_{d,p1,p2,a} \leq inv^{t-1}_{p1,p2,a-1}, \qquad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq MaxAge_{d,p1} \tag{5}$$

Available inventory (in substitution) for (re)distribution to the DNs: same as above, for compatible blood types.

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

Available inventory at each DN for returning to the BC: at each DN, each period's quantity of each blood product and blood type to be returned to the BC equals the inventory that surpassed the DN's respective maximum age.

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

Relation between ordered units from the DNs and (re)distributed units from the BC: at each period, the quantity (re)distributed to the DNs (normal, in substitution or fresh) is restricted to their respective orders.

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

Unmet demand of the BC: at each period, the unmet demand from the BC is calculated by the difference between the ordered quantities from the DNs and the (re)distributed units.

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

$$UDem^{t}_{p1,p2} = \sum_{d} UDem^{t}_{d,p1,p2}, \qquad \forall\, t \geq 1, \forall\, p1, \forall\, p2 \tag{10}$$

Initial inventory update, at the DNs: for each blood product, blood type and age, each period's inventory is established by the sum of the previous inventory and the redistributed units from the BC (for ages between 1 day and the maximum age), by the previous inventory minus the returned units to the BC (for ages between the maximum age and the SL), and by only the previous inventory (for ages older than the SL).

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

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

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

Wasted quantities, at the DNs: each period's wasted units equal the inventory that surpassed its SL.

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

Available inventory, at the DNs, for transfusions: each period's quantity of each blood product and blood type to be transfused to patients is restricted to the available inventory of the DN with ages between 1 day and the DNs' respective maximum ages.

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

Available inventory (in substitution), at the DNs for transfusions: same as above, for compatible blood types.

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

Inventory update after transfusions, at the DNs: for each blood product and blood type, for ages between 1 day and the DNs' respective maximum ages, each period's inventory is updated by retrieving the transfused units to patients, and for ages above the maximum ages, there is no update required.

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

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

Discarded units of blood, at the DNs: for each blood product and blood type, if the total inventory for ages below the SL surpasses the maximum inventory level, the excess units are discarded.

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

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

Maximum inventory levels, at the DNs: for each blood product and blood type, the total inventory for ages below the SL is restricted by the respective maximum inventory level.

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

Final inventory update, at the DNs: for each blood product, blood type and age, each period's inventory is updated by retrieving the discarded units.

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

Safety stock units, at the DNs: for each blood product and blood type, if the inventory with ages between 1 day and the respective DN's maximum age is lower than the minimum level, the safety stock units used are accounted.

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

$$SS\_Units^t_{d,p1,p2} = s^t_{d,p1,p2} \times SS^t_{d,p1,p2}, \qquad \forall\ t, \forall\ d, \forall\ p1, \forall\ p2 \tag{24}$$

Total inventory update, at the DNs: for each blood product and blood type, each period's inventory is the sum of the respective inventory with ages between 1 day and the SL.

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

Ordered quantities, by the DNs: each period's orders quantities of each blood product and blood type are established by the demanded quantity at the same period, minus the still available inventory for the next period, plus the number of safety stock units used, to restore the safety stock at the DNs.

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

Relation between demand and transfused units: for each blood product and blood type, the number of transfusions, for ages between 1 day and the respective DN's maximum age, is restricted to the demand from that period.

$$\sum_{a=1}^{MaxAge_{d,p1}} \left(qDN^t_{d,p1,p2,a} + \sum_{p2'} sDN^t_{d,p1,p2',p2,a}\right) \le DemQt^t_{d,p1,p2}, \qquad \forall\ t, \forall\ d, \forall\ p1, \forall\ p2 \tag{27}$$

Unmet Demand, at the DNs: each period's unmet demand for each blood product and blood type is established by the difference between the demand and the transfused units.

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

Service distance requirement for (re)distributed blood units: for each unit to be (re)distributed to the DNs, it is evaluated if, at the time of arrival to the DNs, the units still have adequate age to be transfused (In the Portuguese case, particularly the LVT region, this is not relevant since only short distances with short driving times are involved).

$$SDR^t_{d,p1,p2,a} = \left(MaxAge_{d,p1} + 1 - a\right) \times \frac{Dist_d}{T_d}, \qquad \forall\ t \ge 1, \forall\ d, \forall\ p1, \forall\ p2, \forall\ a \ge 1 \tag{29}$$

$$S^t_{d,p1,p2,a} = \begin{cases} Dist_d, & if\ Dist_d \le SDR^t_{d,p1,p2,a} \\ 0, & otherwise \end{cases}, \qquad \forall\ t \ge 1, \forall\ d, \forall\ p1, \forall\ p2, \forall\ a \ge 1 \tag{30}$$

Constraints for the binary variables:

$$v^t_{d,p1,p2,a} \times MaxCap \ge rqt^t_{d,p1,p2,a}, \qquad \forall\ t \ge 1, \forall\ d, \forall\ p1, \forall\ p2, \forall\ a \ge 1 \tag{31}$$

$$p^t_{d,p1,p2,a} \times Dist_{max} \ge S^t_{d,p1,p2,a}, \qquad \forall\ t \ge 1, \forall\ d, \forall\ p1, \forall\ p2, \forall\ a \ge 1 \tag{32}$$

$$u^t_{d,p1,p2} \times OrdQt^t_{d,p1,p2} \ge 0, \qquad \forall\ t, \forall\ d, \forall\ p1, \forall\ p2 \tag{33}$$

$$c^t_{d,p1,p2} \times Dis^t_{d,p1,p2} \ge 0, \qquad \forall\ t, \forall\ d, \forall\ p1, \forall\ p2 \tag{34}$$

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

Loads of vehicles, load rates and fuel consumption: depend on the quantity of units being transported**.**

$$L1_d^t = \sum_{p1}\sum_{p2}\sum_{a=1}^{MaxAge_{d,p1}} (p_{d,p1,p2,a}^t \times (qt_{d,p1,p2,a}^t + \sum_{p2'} sqt_{d,p1,p2',p2,a}^t)), \quad \forall\, t \geq 1, \forall\, d \tag{36}$$

$$L2_d^t = \sum_{p1}\sum_{p2}\sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (v_{d,p1,p2,a}^t \times rqt_{d,p1,p2,a}^t), \quad \forall\, t \geq 1, \forall\, d \tag{37}$$

$$L1(2)_d^t \leq MaxL, \quad \forall\, t \geq 1, \forall\, d \tag{38}$$

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

$$Fuel_d^t = CFuel_e + LR1_d^t \times (CFuel_f - CFuel_e) + LR2_d^t \times (CFuel_f - CFuel_e), \quad \forall\, t \geq 1, \forall\, d \tag{40}$$

Refrigeration costs at the BC and at the DNs: depend on the inventory levels for each blood product and blood type.

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

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

Refrigeration costs while driving and unloading: depend on the quantity of each blood product being transported**.**

$$RefriDrv1_d^t = T_d \times \sum_{p1}\sum_{p2}\sum_{a=1}^{MaxAge_{d,p1}} (p_{d,p1,p2,a}^t \times (qt_{d,p1,p2,a}^t + \sum_{p2'} sqt_{d,p1,p2',p2,a}^t) \times CRefri_{p1}), \quad \forall\, t \geq 1, \forall\, d \tag{43}$$

$$RefriDrv2_d^t = T_d \times \sum_{p1}\sum_{p2}\sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (v_{d,p1,p2,a}^t \times rqt_{d,p1,p2,a}^t \times CRefri_{p1}), \quad \forall\, t \geq 1, \forall\, d \tag{44}$$

$$RefriUn_d^t = \sum_{p1}\sum_{p2}\sum_{a=1}^{MaxAge_{d,p1}} (p_{d,p1,p2,a}^t \times (qt_{d,p1,p2,a}^t + \sum_{p2'} sqt_{d,p1,p2',p2,a}^t) \times CRefri_u), \quad \forall\, t \geq 1, \forall\, d \tag{45}$$

Decision variables' domains:

$$inv_{p1,p2,a}^0 = 0, \quad \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq SL_{p1} \tag{46}$$

$$inv_{p1,p2,a}^t \geq 0, \quad \forall\, t \geq 1, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq SL_{p1} \tag{47}$$

$$inv_{p1,p2,a}^t = 0, \quad \forall\, t, \forall\, p1, \forall\, p2, \forall\, a \geq SL_{p1} + 1 \tag{48}$$

$$inv_{p1,p2,0}^t \geq 0, \quad \forall\, t, \forall\, p1, \forall\, p2 \tag{49}$$

$$qt_{d,p1,p2,a}^t \geq 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq MaxAge_{d,p1} \tag{50}$$

$$qt_{d,p1,p2,a}^t = 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq MaxAge_{d,p1} + 1 \tag{51}$$

$$qt_{d,p1,p2,a}^0 = 0, \quad \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{52}$$

$$sqt_{d,p1,p2,p2',a}^t \geq 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, 1 \leq a \leq MaxAge_{d,p1} \tag{53}$$

$$sqt_{d,p1,p2,p2',a}^t = 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq MaxAge_{d,p1} + 1 \tag{54}$$

$$sqt_{d,p1,p2,p2',a}^0 = 0, \quad \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{55}$$

$$p_{d,p1,p2,a}^0 = 0, \quad \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{56}$$

$$p_{d,p1,p2,a}^t \in \{0,1\}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{57}$$

$$inv_{d,p1,p2,a}^t \geq 0, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \leq a \leq SL_{p1} \tag{58}$$

$$inv_{d,p1,p2,a}^t = 0, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq SL_{p1} + 1 \tag{59}$$

$$inv_{d,p1,p2,0}^t = 0, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{60}$$

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

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

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

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

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

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

$$c^{t}_{d,p1,p2} \in \{0,1\}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{67}$$

$$u^{t}_{d,p1,p2} \in \{0,1\}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{68}$$

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

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

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

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

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

$$v^{t}_{d,p1,p2,a} \in \{0,1\}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{74}$$

$$s^{t}_{d,p1,p2} \in \{0,1\}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{75}$$

5.2.3. Objective function

The formulated objective function, described with equation 89, englobes the minimization of all the costs related with the mentioned BSC characteristics, particularly wastage, substitution, disposal, shortage, safety stocks, refrigeration and fuel costs. 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, from the BC to the DNs, and at the level of blood transfusion, at the DNs, so the objective function also englobes the modelling for the FIFO policies. The calculations for the previously considered costs, FIFO policies and the objective function are as follows in equations 76 to 89.

Wastage costs:

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

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

Substitution costs:

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

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

Disposal costs:

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

Shortage costs:

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

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

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:

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

Total 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 for (re)distribution:

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

FIFO policy for transfusion:

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

Objective function:

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

5.2.4. Linearization

As mentioned at the start of section 5.2., the model is formulated as a MINLP problem, with 17 non-linear constraints (equations 2, 8, 9, 11, 12, 17, 20, 24, 26, 33, 34, 35, 36, 37, 43, 44 and 45), since multiplying 2 variables is quite often the most straightforward way of writing constraints. However, in order to solve the model, it needs to be linearized. The linearization of the model, explained below, offers several changes to what was previously mentioned in subsections 5.2.1. and 5.2.2., with the objective function described with equation 89 and the respective considered costs and FIFO policies described with equations 76 to 88, at subsection 5.2.3., remaining the same, considering the changes performed throughout the model. Firstly, for each product between decision variables, a new auxiliar integer decision variable is created, equivalent to the respective product of variables, as presented by equations 90 to 95. Then, several additional linear constraints are applied to the new variables, as presented by equations 96 to 116, to reduce the model's complexity. Finally, the model becomes linearized after the previous non-linear constraints are modified to incorporate the new decision variables, as presented by equations 117 to 132.

- **Auxiliar decision variables**

$a1^t_{d,p1,p2,a}$ → Auxiliary integer variable for the linearization of the multiplication:

$$v^t_{d,p1,p2,a} \times rqt^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{90}$$

$a2^t_{d,p1,p2,a}$ → Auxiliary integer variable for the linearization of the multiplication:

$$p^t_{d,p1,p2,a} \times qt^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{91}$$

$a3^t_{d,p1,p2,p2\prime,a}$ → Auxiliary integer variable for the linearization of the multiplication:

$$p^t_{d,p1,p2,a} \times sqt^t_{d,p1,p2,p2',a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{92}$$

$a4^t_{d,p1,p2}$ → Auxiliary integer variable for the linearization of the multiplication:

$$u^t_{d,p1,p2} \times OrdQt^t_{d,p1,p2}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{93}$$

$a5^t_{d,p1,p2}$ → Auxiliary integer variable for the linearization of the multiplication:

$$c^t_{d,p1,p2} \times Dis^t_{d,p1,p2}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{94}$$

$a6^t_{d,p1,p2}$ → Auxiliary integer variable for the linearization of the multiplication:

$$s^t_{d,p1,p2} \times SS^t_{d,p1,p2}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{95}$$

- **Additional linear constraints**

$a1^t_{d,p1,p2,a}$ → $rqt^t_{d,p1,p2,a}$ is considered to have 0 as lower bound and $MaxCap$ as higher bound.

$$a1^t_{d,p1,p2,a} \leq MaxCap \times v^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{96}$$

$$a1^t_{d,p1,p2,a} \leq rqt^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{97}$$

$$a1^t_{d,p1,p2,a} \geq rqt^t_{d,p1,p2,a} - (1 - v^t_{d,p1,p2,a}) \times MaxCap, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{98}$$

$$a1^t_{d,p1,p2,a} \geq 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{99}$$

$a2^t_{d,p1,p2,a}$ → $qt^t_{d,p1,p2,a}$ is considered to have 0 as lower bound and $MaxCap_d$ as higher bound.

$$a2^t_{d,p1,p2,a} \leq MaxCap_d \times p^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{100}$$

$$a2^t_{d,p1,p2,a} \leq qt^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{101}$$

$$a2^t_{d,p1,p2,a} \geq qt^t_{d,p1,p2,a} - (1 - p^t_{d,p1,p2,a}) \times MaxCap_d, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{102}$$

$$a2^t_{d,p1,p2,a} \geq 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, a \geq 1 \tag{103}$$

$a3^t_{d,p1,p2,p2\prime,a}$ → $sqt^t_{d,p1,p2,p2',a}$ is considered to have 0 as lower bound and $MaxCap_d$ as higher bound.

$$a3^t_{d,p1,p2,p2\prime,a} \leq MaxCap_d \times p^t_{d,p1,p2,a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{104}$$

$$a3^t_{d,p1,p2,p2\prime,a} \leq sqt^t_{d,p1,p2,p2',a}, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{105}$$

$$a3^t_{d,p1,p2,p2\prime,a} \geq sqt^t_{d,p1,p2,p2',a} - (1 - p^t_{d,p1,p2,a}) \times MaxCap_d, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{106}$$

$$a3^t_{d,p1,p2,p2\prime,a} \geq 0, \quad \forall\, t \geq 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, p2', \forall\, a \geq 1 \tag{107}$$

$a4^t_{d,p1,p2}$ → $OrdQt^t_{d,p1,p2}$ is considered to have $-MaxCap_d$ as lower bound and $MaxCap_d$ as higher bound.

$$-MaxCap_d \leq a4^t_{d,p1,p2} \leq MaxCap_d, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{108}$$

$$-MaxCap_d \times u^t_{d,p1,p2} \leq a4^t_{d,p1,p2} \leq MaxCap_d \times u^t_{d,p1,p2}, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{109}$$

$$OrdQt^t_{d,p1,p2} - (1 - u^t_{d,p1,p2}) \times MaxCap_d \leq a4^t_{d,p1,p2} \leq OrdQt^t_{d,p1,p2} + (1 - u^t_{d,p1,p2}) \times MaxCap_d, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{110}$$

$a5^t_{d,p1,p2}$ → $Dis^t_{d,p1,p2}$ is considered to have $-MaxCap_d$ as lower bound and $MaxCap_d$ as higher bound.

$$-MaxCap_d \le a5^t_{d,p1,p2} \le MaxCap_d, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{111}$$

$$-MaxCap_d \times c^t_{d,p1,p2} \le a5^t_{d,p1,p2} \le MaxCap_d \times c^t_{d,p1,p2}, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{112}$$

$$Dis^t_{d,p1,p2} - (1 - c^t_{d,p1,p2}) \times MaxCap_d \le a5^t_{d,p1,p2} \le Dis^t_{d,p1,p2} + (1 - c^t_{d,p1,p2}) \times MaxCap_d, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{113}$$

$a6^t_{d,p1,p2}$ → $SS^t_{d,p1,p2}$ is considered to have $-MaxCap_d$ as lower bound and $MaxCap_d$ as higher bound.

$$-MaxCap_d \le a6^t_{d,p1,p2} \le MaxCap_d, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{114}$$

$$-MaxCap_d \times s^t_{d,p1,p2} \le a6^t_{d,p1,p2} \le MaxCap_d \times s^t_{d,p1,p2}, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{115}$$

$$SS^t_{d,p1,p2} - (1 - s^t_{d,p1,p2}) \times MaxCap_d \le a6^t_{d,p1,p2} \le SS^t_{d,p1,p2} + (1 - s^t_{d,p1,p2}) \times MaxCap_d, \quad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{116}$$

- **Modified constraints**

$$inv^t_{p1,p2,a} = inv^{t-1}_{p1,p2,a-1} + \\ + \sum_d (a1^t_{d,p1,p2,a} - a2^t_{d,p1,p2,a} - \sum_{p2'} a3^t_{d,p1,p2,p2',a}), \quad \forall\, t \ge 1, \forall\, p1, \forall\, p2, \forall\, 1 \le a \le SL_{p1} \tag{117}$$

$$\sum_{a=1}^{MaxAge_{d,p1}} (a2^t_{d,p1,p2,a} + \sum_{p2'} a3^t_{d,p1,p2',p2,a}) \le a4^{t-1}_{d,p1,p2}, \qquad \forall\, t \ge 1, \forall\, d, \forall\, p1, \forall\, p2 \tag{118}$$

$$UDem^t_{d,p1,p2} = aux4^{t-1}_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}} (aux2^t_{d,p1,p2,a} + \sum_{p2'} aux3^t_{d,p1,p2',p2,a}), \qquad \forall\, t \ge 1, \forall\, d, \forall\, p1, \forall\, p2 \tag{119}$$

$$InvAux^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1} + a2^t_{d,p1,p2,a} + \sum_{p2'} a3^t_{d,p1,p2,p2',a}, \\ \forall\, t \ge 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, 1 \le a \le MaxAge_{d,p1} \tag{120}$$

$$InvAux^t_{d,p1,p2,a} = inv^{t-1}_{d,p1,p2,a-1} - a1^t_{d,p1,p2,a}, \quad \forall\, t \ge 1, \forall\, d, \forall\, p1, \forall\, p2, \forall\, MaxAge_{d,p1} + 1 \le a \le SL_{p1} \tag{121}$$

$$\sum_{a=1}^{SL_{p1}} disqt^t_{d,p1,p2,a} = a5^t_{d,p1,p2}, \qquad \forall\, t, \forall\, p1, \forall\, p2 \tag{122}$$

$$OrdQt^t_{d,p1,p2} = DemQt^t_{d,p1,p2} - \sum_{a=1}^{MaxAge_{d,p1}-1} \left(inv^t_{d,p1,p2,a}\right) + a6^t_{d,p1,p2}, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{123}$$

$$a4^t_{d,p1,p2} \ge 0, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{124}$$

$$a5^t_{d,p1,p2} \ge 0, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{125}$$

$$a6^t_{d,p1,p2} \ge SS^t_{d,p1,p2}, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{126}$$

$$SS\_Units^t_{d,p1,p2} = a6^t_{d,p1,p2}, \qquad \forall\, t, \forall\, d, \forall\, p1, \forall\, p2 \tag{127}$$

$$L1^t_d = \sum_{p1}\sum_{p2} \sum_{a=1}^{MaxAge_{d,p1}} (a2^t_{d,p1,p2,a} + \sum_{p2'} a3^t_{d,p1,p2,p2',a}), \qquad \forall\, t \ge 1, \forall\, d \tag{128}$$

$$L2^t_d = \sum_{p1}\sum_{p2} \sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (a1^t_{d,p1,p2,a}), \qquad \forall\, t \ge 1, \forall\, d \tag{129}$$

$$RefriDrv1_d^t = T_d \times \sum_{p1}\sum_{p2}\sum_{a=1}^{MaxAge_{d,p1}} ((a2_{d,p1,p2,a}^t + \sum_{p2'} a3_{d,p1,p2,p2',a}^t) \times CRefri_{p1}), \quad \forall\, t \geq 1, \forall\, d \tag{130}$$

$$RefriDrv2_d^t = T_d \times \sum_{p1}\sum_{p2}\sum_{a=MaxAge_{d,p1}+1}^{SL_{p1}} (a1_{d,p1,p2,a}^t \times CRefri_{p1}), \quad \forall\, t \geq 1, \forall\, d \tag{131}$$

$$RefriUn_d^t = \sum_{p1}\sum_{p2}\sum_{a=1}^{MaxAge_{d,p1}} ((a2_{d,p1,p2,a}^t + \sum_{p2'=0}^{P2} a3_{d,p1,p2,p2\prime,a}^t) \times CRefri_u), \quad \forall\, t \geq 1, \forall\, d \tag{132}$$

5.3. Main chapter conclusions

This chapter presented the formulation of the inventory management and distribution & collection model developed, which is to be analyzed in the next chapter. Its main goal is to achieve sustainability, by reducing total costs which englobe the three main sustainability aspects – economic, social and environmental –, by considering the necessary calculations and constraints. Firstly, it was presented a MINLP formulation that was then linearized into a MILP model, to reduce its complexity. Table 11 presents the two formulations and their respective equations.

Table 11 – MINLP and MILP formulated models.

Model	**MINLP**	**MILP**	
Calculations & Constraints	(1) – (75)	(1) (117) (3) – (7) (118) – (119) (10) (120) – (121) (13) – (19) (122) (21) – (23)	(123) (25) (124) (27) – (32) (125) – (129) (38) – (42) (130) – (132) (46) – (75) (96) – (116)
Objective Function	(76) – (89)		

6. Results and discussion

In this chapter, the model formulated in chapter 5 is applied and tested, and the results are analyzed and discussed. Firstly, section 6.1. presents all the data and assumptions considered. Then, section 6.2. enumerates the performance indicators to be evaluated with the results, which are then presented at section 6.3. and discussed in comparison with the model without returning and redistribution of units. Section 6.4. performs a sensitivity analyses focused on the SL of the managed blood product at the model. Finally, after the analyses on the results, this chapter ends with section 6.5. presenting its main conclusions.

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.

This section presents the assumptions made and the data used for the model. As it is clear from the model's formulation, there are many input parameters to add initially. The initial parameters, such as the mentioned costs, inventory levels and maximum capacities, as well as the considered BC and the DNs, are explored from IPST's sources as far as possible. However, there is limited official information on some 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.

- **Costs**

There are 6 different types of costs considered in this model - wastage, disposal, shortage, safety stock, substitution, and refrigeration costs – assumed as follows.

The wastage costs occur when blood units in storage surpass their respective SL and become unfit for transfusions or (re)distribution. Since wastage of blood is to be minimized as far as possible, the value for the wastage costs should be sufficiently high. Additionally, the wastage cost of each blood type is assumed to be different due the various compatibilities among them. For instance, blood type O-, known as the universal donor, is considered as the most needed and important blood type since it can fulfill all demand. Consequently, the waste cost of this blood type is assumed to be higher. According to the compatibility and priority orders for substitutions, illustrated in table 8 from chapter 3, the descending order of preference and thus wastage costs is the following: O-, B-, A-, O+, AB-, B+, A+ and AB+. According to a source from IPST, wastage costs should be around 15% of the total cost of production of the blood product. Once that 214,40 €/pool is the production cost of pools of PLTs with PR for the Portuguese BSC, the total wastage cost is approximately 32 €/pool. Considering the order of compatibility and preference described previously, 32 €/pool is assumed for the least compatible blood type, AB+, and then 10€ are constantly added to the next most compatible blood type, meaning that for O-, the most compatible and preferred blood type, the wastage cost is considered to be 102 €/pool, as presented at table 12.

Disposal costs, also presented at table 12, are similar to the wastage costs. However, these occur when units of blood with ages below the SL have to be wasted due to the maximum capacity of the storage facility being surpassed. Since these units are still fit for transfusions or (re)distributions, their wastage is more critical, so the disposal costs are assumed to be higher than the wastage costs, particularly 50€ more than the wastage costs, for each blood type.

As for the shortage costs, these occur when there is unmet demand at the level of (re)distribution, when the DNs demand is not met by the BC, and at the level of transfusion of blood, when the patients' demands are not met by the DNs. In reality, not all procedures are urgent, and so the transfusion of blood units can be postponed. In addition, in case there is an urgent procedure and lack of blood units, hospitals can get blood units from other sources (Meneses, 2019). To simplify, these details are ignored in the present model. Since the shortage of blood can compromise the patients' health, its costs should be high. Meneses (2019), Dillon et al. (2017) and Gunpinar & Centeno (2015) considered 1340 €/unit as the shortage cost, for RBCs. Hence, similar values are used for this model, for both the BC and the DNs, as presented at table 12: for AB+, it is assumed 1300 €/pool, and then 10€ are added to the next blood types, following the considered order of compatibility and preference.

Concerning the safety stock costs, these occur when the inventory at the DNs falls below the respective minimum inventory imposed by the facility. This is a fictitious cost to avoid shortage and so there is no official information from IPST on this. Hence, the values presented at table 12 are assumed as the safety stock costs for this work, for pools of PLTs with PR, per blood type, for the DNs, and follow the order of compatibility and preference described previously for the other costs.

Table 12 – Wastage, disposal, shortage and safety stock costs, for pools of PLTs with PR, per blood type.

	Blood Types							
Costs	**O-**	**O+**	**A-**	**A+**	**B-**	**B+**	**AB-**	**AB+**
Wastage	102 €/unit	72 €/unit	82 €/unit	42 €/unit	92 €/unit	52 €/unit	62 €/unit	32 €/unit
Disposal	152 €/unit	122 €/unit	132 €/unit	92 €/unit	142 €/unit	102 €/unit	112 €/unit	82 €/unit
Shortage	1.370 €/unit	1.340 €/unit	1.350 €/unit	1.310 €/unit	1.360 €/unit	1.320 €/unit	1.330 €/unit	1.300 €/unit
Safety Stock	50 €/unit	35 €/unit	40 €/unit	20 €/unit	45 €/unit	25 €/unit	30 €/unit	15 €/unit

Regarding the substitution costs, these occur when there are blood type substitutions, both for the (re)distribution, from the BC to the DNs, and for the transfusion of blood products, at the DNs. Substitutions are accepted by the DNs and can happen in case there is shortage in the required blood type. However, the transfusion of the identical blood type is usually preferred and considered as good practice by the demand nodes (Meneses, 2019). Thus, the substitutions costs are calculated according to the shortage costs and depend on the substitution's priority matrix presented previously at chapter 5 – the least favorable substitutions are more expensive, as they the baseline cost, while the most favorable substitutions are cheaper (the baseline cost divided by the level of preference). That said, the assumed baseline cost for blood type substitutions is 500€ and 600€, for the (re)distribution of blood from the BC to the DNs and at the DNs, respectively. Given that it is considered as good practice by the DNs to transfuse identical blood types, then the baseline cost for substitutions at the DNs is assumed higher.

Lastly, refrigeration is extremely important to keep blood products at the required temperature conditions to prevent them from deteriorating until their respective expiry date. The related costs for refrigeration are accounted at three situations – storage, transportation and unloading. When in storage at the BC, refrigeration costs are accounted

for each blood unit kept in inventory after (re)distribution at the DNs and the arrival of new blood units from donations. At the DNs, refrigeration costs are accounted after (re)distribution and the transfusions to meet patients' demand. During transportation, refrigeration also needs to take place, and so the distribution vehicles need to be prepared to keep blood units refrigerated throughout the entire travel until reaching the final destination. When unloading the blood units at the BC or at the DNs, refrigeration is also very critical to maintain the storage temperature in order to preserve the freshness of both the unloaded blood and the loaded blood.

Meneses (2019) considered 1,1 €/unit/day as the refrigeration/storage cost at the DNs, for RBCs, whose ideal storage temperature is between 2 to 10 ºC. For PLTs, whose ideal storage conditions imply a temperature between 20 to 24 ºC (room temperature) and constant agitation, a lower value of 1€/unit/day is considered for the refrigeration cost at the BC and the DNs, accounting for the crucial constant agitation needed in storage for this blood product. During transportation, the refrigeration cost can be assumed to be higher, such as 1,5 €/unit/day. When unloading, due to the opening of the vehicles' doors and compartments, the temperature of the air inside might change as the air outside flows in. So, to keep the storage temperature unchanged, more temperature control needs be done, which obviously increases the costs. Hence, the unloading refrigeration cost is assumed to be 2 €/unit.

- **The vehicles:**

As stated in section 2.3.4, there is limited official information on the distribution of blood by IPST and on the type of distribution vehicles used in Portugal. Hence, assumptions need to be made.

As for the fuel consumption of the distribution vehicles, as formulated in chapter 5, it is calculated considering the loas rates in each travel and the fuel consumption cost of the vehicles when empty and when with full load. From an IPST source, it is known that 0,14 €/km is approximately the fuel consumption cost for the Portuguese distribution vehicles. That said, 0,14 €/km is the considered value for the fuel consumption cost of the distribution vehicles, when with full load. When empty, this parameter is calculated according to the price of the fuel in Portugal (approximately 1,9 €/l) and to the considered type of distribution vehicles used, assumed to be similar to those used in nearby European countries, such as the United Kingdom. One of the vehicles found as a possible blood transportation vehicle, from literature research, was the *Ford Transit Courier*, with an average consumption of 4 liters per 100 kilometers (Motoreu, 2016). Hence, 0,08 €/km is the assumed value for the fuel consumption cost of the vehicles when empty.

Regarding the maximum load of the vehicles, blood distribution vehicles can be assumed similar to those used in nearby European countries, such as the United Kingdom. That said, one of the vehicles found as a possible blood (and even organ) transportation vehicle, from literature research, was the *Ford Transit Courier*. The maximum load of the vehicles is also assumed according to the vehicle's luggage compartment capacity, which is approximately 500 kg (Motoreu, 2016). Counting with the weight and space of the refrigeration and storage equipment, it can be assumed that the remaining luggage capacity of the vehicles is less, assuming around 400 kg. Considering that each blood bag/unit has 450 ml and that 1 ml of blood weights around 1,06 g, each blood unit weights around 0,5 kg, which means that the distribution vehicles have an assumed maximum luggage capacity of 800 blood units.

It is important to refer that, in reality, the distribution and collection of blood usually takes place in a single trip with a single vehicle, starting at the BC and passing through the desired DNs, and so the maximum capacity of the vehicles has to be respected along the entire route. However, in this work the routes are accounted separately - one

vehicle for each travel -, which also translates in higher fuel, damage and refrigeration costs. Hence, 800 blood units becomes a very high value for the maximum load of the vehicles in this case, since the quantities transported to and from one only DN will never reach this maximum value. Yet, these values are still considered for this model despite this difference from reality and the results will take these details into consideration when analyzing the total costs.

- **The BC and the DNs:**

As mentioned previously, this model is to be applied to the Portuguese case, particularly CSTL, which manages 3 regions: LVT, with 14 DNs and including 28 hospitals, Alentejo, with 4 DNs including 5 hospitals, and Algarve, with only 1 DN including 3 hospitals (Serviço Nacional de Saúde, 2022a). This work focuses on the DNs from the LVT region, particularly 5 hospitals. The approximate driving distances from the BC to each DN are calculated using *Google Maps*, as well as the respective driving time, according to the travel route taken and to the hours assumed for the (re)distribution (8 am). Table 13 presents these data.

- **SL and maximum age of PLTs:**

The PLTs' SL is determined by country regulations to detect and prevent bacterial contamination. For instance, in the United States it is limited to 5 days, 3 days in Japan, and up to 7 days in most European Union countries (Pirabán et al., 2019). Hence, 7 days is the considered as the SL of PLTs, so units older than 7 days of age are no longer suitable for transfusion. 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. So, considering that other countries use a younger age than 7 days as the maximum age for PLTs, that the more storage days the more risk of contamination and, consequently, negative effects for patients, that fresher transfused blood leads to better results in some patients and the possibility of redistribution of blood units, the consideration of different maximum ages for the transfusion of PLTs at the DNs is here assumed, according to the specialties and types of treatments performed at each DN. PLTs are used to prevent or treat bleeding in patients with low PLT count or functional PLT disorders, and for cancer treatments and organ transplants, as mentioned in table 9. Hence, to differentiate the DNs considered in this study, it is assumed that DNs specialized in oncology require a much lower maximum age of PLTs, of 2 days. DNs with a wider range of medical specialties and emergency services are assumed to have higher maximum ages of PLTs, of 5 or 7 days. The remaining DNs are assumed to require maximum ages of 3 or 4 days.

Table 13 – The considered DNs, driving distances and driving times from CSTL (according to *Google Maps*) and maximum ages for pools of PLTs with PR.

DNs		Driving Distance (from CSTL)	Driving Time (from CSTL)	Maximum age for 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 (IPO) de Lisboa, EPE	5,3 km	15 min	2 days

- **Demand levels:**

IPST provides data on the daily number of the various blood products distributed from the CSTs to the DNs, from the year 2000 until 2019. Since there is no official data on each DN's demand, the IPST data on the number of

distributed units to the DNs are here assumed to be the demanded units. By restricting the IPST data to December of 2019, to pools of PLTs and to the DNs from the Portuguese LVT region, the daily demanded quantities at the 5 considered DNs are obtained, as presented at tables 14 to 18. The non-presented blood types or days of the month are the ones with zero demand.

Table 14 - Demand of pools of PLTs w/ PR, at DN A (*S. José*), in December of 2019.

DN A – S. José																									
Day	Blood Types							Day	Blood Types							Day	Blood Types								
	O-	O+	A-	A+	B-	B+	AB+		O-	O+	A-	A+	B-	B+	AB+		O-	O+	A-	A+	B-	B+	AB+		
1	0	1	1	1	0	0	0	11	0	2	1	0	0	0	0	21	0	2	0	2	0	0	0		
2	1	1	1	5	0	0	0	12	2	3	1	0	1	0	0	22	1	1	0	2	0	0	0		
3	0	3	0	3	0	0	0	13	0	1	1	3	0	4	1	23	0	1	1	3	0	0	0		
4	1	3	0	4	0	0	0	14	3	2	0	3	0	1	0	25	0	1	0	7	0	0	0		
5	0	2	0	0	0	0	0	16	0	2	1	5	0	0	0	26	1	3	0	4	0	1	0		
6	0	2	0	2	0	1	0	17	0	5	0	4	0	0	1	27	1	3	0	4	0	1	1		
7	0	2	1	2	0	1	0	18	1	5	0	4	0	0	0	28	1	4	1	4	0	0	0		
8	0	2	1	2	0	1	0	19	1	3	0	4	0	2	0	29	0	2	0	0	0	0	0		
9	0	4	0	1	0	0	0	20	0	3	0	6	1	1	0	30	1	6	0	4	0	0	0		
10	0	2	0	0	0	0	0																		

Table 15 - Demand of pools of PLTs w/ PR, at DN B (*Sta. Maria*), in December of 2019.

DN B – Sta. Maria																									
Day	Blood Types							Day	Blood Types							Day	Blood Types								
	O-	O+	A-	A+	B+	AB+			O-	O+	A-	A+	B+	AB+			O-	O+	A-	A+	B+	AB+			
1	1	2	0	4	2	1	12	0	8	0	5	4	1	22	0	1	0	1	1	0					
2	0	8	0	5	0	0	13	1	10	0	2	0	0	23	0	7	0	5	1	0					
3	0	6	2	1	1	0	14	0	4	0	4	0	0	24	1	2	0	2	0	0					
4	2	4	1	2	0	0	15	0	3	0	1	1	2	25	2	4	0	3	1	0					
5	0	7	0	5	0	0	16	1	10	0	5	1	0	26	0	0	1	2	1	0					
6	0	5	2	6	2	0	17	1	5	0	4	0	0	27	0	10	1	4	0	0					
7	0	3	0	3	0	0	18	1	4	1	6	0	0	28	2	0	5	9	0	0					
8	0	4	1	2	2	0	19	0	8	1	3	0	0	29	4	5	0	3	0	0					
9	1	4	3	10	1	0	20	0	5	2	2	0	1	30	1	8	2	5	0	0					
10	1	7	1	4	1	0	21	2	5	0	0	1	0	31	0	5	0	2	0	0					
11	3	5	2	0	1	0																			

Table 16 - Demand of pools of PLTs w/ PR, at DN C (*S. F. Xavier*), in December of 2019.

DN C – S. Francisco Xavier																									
Day	Blood Types							Day	Blood Types							Day	Blood Types								
	O-	O+	A-	A+	B+				O-	O+	A-	A+	B+				O-	O+	A-	A+	B+				
2	0	0	0	1	0	14	0	0	0	3	0	22	0	1	0	1	0								
3	0	0	0	1	0	15	0	1	0	0	1	23	0	1	1	0	0								
4	0	0	0	1	1	16	0	1	0	1	0	25	0	0	1	1	0								
5	1	0	0	1	0	17	0	0	0	2	0	26	0	0	1	1	0								
6	0	0	0	2	0	18	0	1	0	0	0	27	0	0	0	2	0								
8	0	0	1	2	0	19	0	1	0	0	0	29	0	1	1	0	0								
10	0	2	0	2	0	20	0	0	1	1	1	30	0	1	0	0	0								
11	0	1	0	0	0	21	1	0	0	0	0	31	0	2	0	0	0								
12	0	0	1	1	0																				

Table 17 - Demand of pools of PLTs w/ PR, at DN D (*Amadora-Sintra*), in December of 2019.

DN D – Amadora-Sintra																									
Day	Blood Types							Day	Blood Types							Day	Blood Types								
	O-	O+	A-	A+	B+				O-	O+	A-	A+	B+				O-	O+	A-	A+	B+				
1	0	0	1	1	0	9	1	0	0	1	0	23	0	1	0	0	1								
2	0	2	0	0	0	11	0	1	0	0	0	26	0	2	0	0	0								
3	0	0	0	2	0	12	0	1	0	0	0	27	0	1	0	0	0								
4	1	0	0	0	0	13	0	0	0	1	0	28	0	0	0	1	0								
5	0	1	0	0	0	16	1	1	0	1	0	29	0	0	0	1	0								
6	0	1	0	0	0	18	0	0	0	1	0	30	0	1	0	0	0								
7	0	0	1	0	0	20	1	0	0	1	0	31	0	1	0	2	0								
8	0	0	0	1	0	22	0	0	0	1	0														

Table 18 - Demand of pools of PLTs w/ PR, at DN E (IPO), in December of 2019.

DN E – IPO																						
Day	Blood Types						Day	Blood Types						Day	Blood Types						
	O-	O+	A-	A+	B+	AB+		O-	O+	A-	A+	B+	AB+		O-	O+	A-	A+	B+	AB+		
3	0	6	1	1	1	0	12	0	2	0	8	0	0	23	1	10	1	6	1	1		
4	0	6	2	6	1	0	13	1	6	0	1	0	0	24	0	1	2	5	0	0		
6	2	4	0	5	1	0	14	0	3	1	1	0	0	26	0	1	2	1	0	0		
7	0	5	0	5	1	0	16	2	6	3	9	0	0	27	0	4	0	6	1	0		
8	3	3	1	0	0	0	18	0	4	0	1	1	0	29	1	5	0	2	1	1		
9	1	3	1	8	0	1	19	1	5	1	2	0	0	30	2	6	1	5	1	1		
11	1	2	0	7	0	0	20	2	1	0	7	0	1	31	0	2	0	1	0	1		

- **Supply levels:**

IPST provides daily data on the collection of WB since the year 2000 until 2019, from all the Portuguese regions. With the data from December of 2019, in the regions covered by CSTL, the same data for pools of PLTs can be calculated using the collection and production numbers from 2019, retrieved from Escoval et al. (2020). In 2019, 310311 was the total number of donations, and 9987 was the number of produced pools of PLTs with PR, which can be translated into the fact that 3,22% of the collected WB was produced into pools of PLTs with PR. By multiplying the collection data for WB using this percentage, the approximate (by excess) daily supplied number of pools of PLTs with PR, at the CSTL, from December of 2019, can be obtained.

However, it is important to note that the CSTL works with more DNs than the ones considered. Hence, certain supplied quantities to the CSTL are to be managed, (re)distributed and used by the other DNs, besides the considered ones. That said, by knowing the DNs from the region of operation of the CSTL that are not considered in the model and its levels of demand, an approximate quantity of blood can be retrieved from the total supplied quantities to the CSTL, in order to avoid wastage or, even if undesired, zero shortage, due to overstock. In fact, only 63,05% of the total demanded units of pools of PLTs from December of 2019 are known to be allocated to the DNs considered in the case study. Hence, 63,05% of the total supplied units are considered as the levels of supply. The approximate (in excess) supply of pools of PLTs with PR, to the CSTL, to be managed by the 5 considered DNs at this model, is as presented in table 19.

Table 19 – Supply of pools of PLTs w/ PR, in December of 2019 (to be managed by the 5 DNs considered in this model).

Day	Blood Types								Day	Blood Types							
	O-	O+	A-	A+	B-	B+	AB-	AB+		O-	O+	A-	A+	B-	B+	AB-	AB+
1	7	42	8	48	1	5	0	2	16	7	19	3	14	0	4	0	1
2	4	9	4	16	1	3	0	3	17	3	14	4	13	1	2	1	2
3	4	16	4	11	1	4	1	1	18	5	17	4	21	1	4	2	2
4	4	11	4	9	0	2	1	2	19	2	17	5	22	1	3	1	3
5	5	14	4	13	1	4	1	1	20	5	9	1	11	1	3	1	2
6	5	30	8	21	1	3	0	1	21	9	25	5	31	1	9	1	4
7	8	23	7	30	1	5	0	2	22	8	29	4	18	1	9	1	2
8	9	28	9	26	1	5	0	2	23	3	24	5	23	3	4	2	3
9	5	12	5	14	1	2	1	2	24	2	5	2	4	0	0	0	0
10	6	14	3	21	1	5	1	2	26	4	20	4	17	0	2	0	3
11	2	14	4	15	1	4	0	2	27	6	31	6	29	3	4	0	4
12	3	15	2	19	1	4	1	2	28	5	25	5	24	2	7	1	1
13	4	15	5	20	1	2	1	1	29	2	6	2	5	0	2	0	1
14	5	17	3	19	1	5	0	3	30	5	25	3	29	2	5	0	2
15	9	42	7	45	1	8	1	4	31	2	8	1	7	1	2	0	1

- **Minimum, satisfactory and maximum inventory levels of the DNs:**

According to IPST recommendations and to IPST's Contingency Plan for sustainability and safety of the supply of blood and blood products at the CSTs (Serviço Nacional de Saúde, 2022b), the minimum inventory level of blood products at the DNs is that there should be enough quantity for 4 days of normal demand, and is calculated using the average supply over the last 90 days (so, approximately October and November of 2019) multiplied by 4. The satisfactory inventory level follows the same logistics, but for 7 days of normal demand. This is assumed for pools of PLTs with PR. Thus, tables 20 and 21 present the two inventory levels, minimum and satisfactory, respectively, for the considered DNs, per blood type (the values are rounded up). Although these levels are updated daily, to simplify, in this work it is assumed the same over the entire planning horizon.

Table 20 – Minimum inventory level of pools of PLTs w/ PR, at the considered DNs, per blood type.

Blood Types	DNs				
	A	**B**	**C**	**D**	**E**
O-	1	3	1	1	1
O+	5	12	2	2	8
A-	1	2	1	1	1
A+	6	14	2	2	7
B-	1	1	0	0	1
B+	1	3	1	1	2
AB-	0	0	0	0	0
AB+	1	1	1	0	1

Table 21 – Satisfactory inventory level of pools of PLTs w/ PR, at the considered DNs, per blood type.

Blood Types	DNs				
	A	**B**	**C**	**D**	**E**
O-	2	4	1	1	1
O+	9	21	4	3	13
A-	1	3	0	1	2
A+	10	24	4	3	11
B-	1	1	0	0	1
B+	2	4	1	1	2
AB-	0	0	0	0	0
AB+	1	2	1	1	1

Lastly, the maximum inventory levels depend on the capacity of the different facilities. Meneses (2019) considered 80 for O-, 120 for O+, 60 for A-, 150 for A+, 40 for B+ and 10 for B-, AB- and AB+, as the maximum inventory in the case study. There is no official information on the maximum capacities of the considered DNs in this work for pools of PLTs with PR. So, although in the model by Meneses (2019) RBCs is the blood product in question, here the maximum inventory levels are assumed the same as the ones by Meneses (2019). As for the maximum capacity of the CSTL, there is also no official information from the CSTL, so an assumed value of 1400 units is considered.

Table 22 – Maximum inventory of pools of PLTs with PR, at the CSTL and the DNs.

Facility	Blood Types							
	O-	**O+**	**A-**	**A+**	**B-**	**B+**	**AB-**	**AB+**
DNs	80	120	60	150	10	40	10	10

- **Initial inventory levels of the DNs:**

There is no available official information with the levels of inventory for December of 2019. Hence, the satisfactory levels of inventory previously mentioned, and presented in table 22, are used as the initial inventory levels of the DNs, for the first day of December of 2019.

In this work's formulated model, the inventory levels are divided per blood product, per blood type and per age. So, the assumed initial values of inventory at the DNs are divided per age and considering the FIFO policy for transfusion, which means more units with younger ages than with older ages in inventory. Also, because of the additional parameter for the maximum age of blood products transfused by the DNs, their initial inventory numbers are only divided by ages below or equal to the maximum age, leaving the older ages with zero initial inventory.

6.2. Performance indicators

KPIs are key indicators used to evaluate the performance of the model and the quality of its results (Meneses, 2019). Firstly, since the main goal of the formulated model is the minimization of the total costs, then the final value of the objective function becomes an important KPI for this model, to understand whether the model is cost-effective and outputs quality results. Then, to understand if the model is sustainable and prevents wastage, assessing the waste levels becomes crucial, since its minimization is what is desired. Hence, it is also a very important KPI of the model to evaluate its performance. That said, the levels of returned non-fresh units from the DNs to be redistributed to other DNs can influence the levels of waste and are important to understand if the consideration of maximum ages for the blood handled by the DNs is advantageous and results in waste minimization, as well as shortage minimization. The evaluation of the daily inventory levels is also important, since if it is too high it can result in more waste of blood in inventory, but, if too low it can lead to shortage of blood for distribution and for transfusions. So, the inventory levels should guarantee both the minimization of waste and the maximization of service. Hence, the shortage levels, the levels of returned units and the daily inventory levels are also important KPIs. Blood type substitutions levels are also important KPIs to analyze, once that substitutions occurs when there is shortage of the desired blood types, and for some patients and treatments it might not be desired to perform substitutions. Lastly, the age of the transfused units at the DNs is an important KPI to evaluate the quality of the service, since, as mentioned in section 6.1., the more storage days the more risk of contamination and because some studies show that the freshness of transfused blood units may lead to better results in some patients (Hosseinifard & Abbasi, 2018). So, it is important to evaluate what is the model's impact on this matter. In short, the KPIs to be analyzed are: total costs, waste levels, levels of returned non-fresh units, shortage levels, substitution levels, daily inventory levels and the age of transfused units.

6.3. Results

This section's purpose is to present and analyze the model's results, leaned on the Portuguese BSC, with all the sets, parameters and assumptions presented in section 6.1. The planning horizon considered was 31 days (the entire month of December of 2019). Additionally, for comparison purposes, the model is tested without the possibility of redistribution of blood. In order to do that, the group of parameters and constraints (equations 7, 31, 38, 39, 40, 69, 70, 71, 72, 73, 74, 86, 96, 97, 98, 99, 117, 121, 129 and 131) on the redistribution and returning of blood products were removed/modified from the model. In this case, since there is no return of blood units from the DNs back to the BC, 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.

The model was implemented in Python language and using the IBM ILOG CPLEX 22.1.0.0 solver, on a computer equipped with a 2.00 GHz Intel® Core i3 processor and 8 GB of RAM. For the formulated model (*Model 1 – Redistribution & Returns*), it was run for 9002 seconds (about 2 and a half hours), and presented a feasible solution with a gap of 3,5%. For the modified model (*Model 2 – Close-to-Reality*), it was run for 5401 seconds (about 1 and a half hours), and presented a feasible solution with a gap of 3.1%.

- **Total costs:**

The total costs (except for the FIFO policies) of the two models are presented in table 23. From that, it is possible to infer that total cost resulting from model 1 is higher than model 2. However, it is only significantly costlier for the refrigeration costs. Model 2 presents higher costs of wastage, substitution and safety stocks. The remaining costs are the same for the two models. That said, it is possible to infer that with model 2, which does not consider returning and redistributing blood units, 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. Lastly, for both models there is no disposal of blood units and the shortage levels and fuel costs are the same.

Table 23 – Total wastage, disposal, substitution, shortage, safety stocks, fuel and refrigeration costs.

	Costs (€)							
Model	Wastage	Disposal	Substitution	Shortage	Safety Stocks	Fuel	Refrigeration	Total
1	45.622	0	1.772	12.020	25.305	92	12.731	97.542
2	46.020	0	2.398	12.020	25.720	92	11.123	97.373

- **Wastage levels:**

Model 2 presents higher costs of wastage, suggesting that there is more wastage without redistribution of blood. In total, model 1 prevents the waste of 9 units of blood: for model 1 the total wastage is 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. 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, which would lower 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. Figures 18 and 19 display graphical representations of the wastage levels throughout the month, at the BC and at the DNs, for both models.

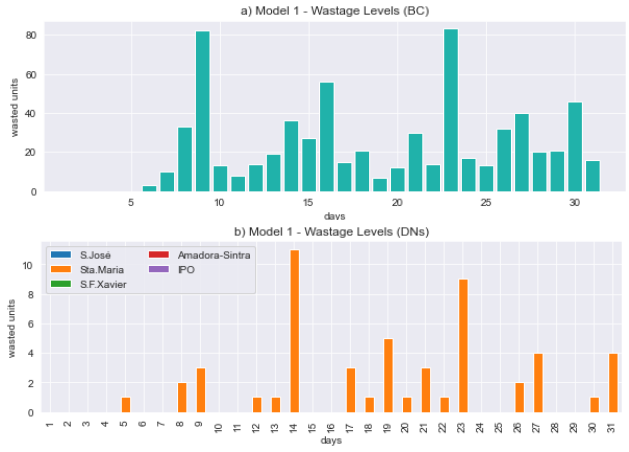

Figure 18 – Wastage levels for model 1:
a) at the BC, and b) at the DNs.

Figure 19 – Wastage levels for model 2:
a) at the BC, and b) at the DNs.

- **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, as it is clear from figure 20 that graphically shows the levels of returned units throughout the month, from all the DNs.

Returned units can only be redistributed at the period after being returned, and so, 1 day older. Hence, the units returned from DN E (*IPO*) have the chance to be redistributed to all the remaining DNs, except for DN C (*S. F. Xavier*) which has a maximum age of 3 days (DN E returns units with 3 days of age and so at the next period, with 4 days of age, these are no longer suited to be used by DN C). Likewise, blood units returned from DN C (*S. F. Xavier*) can only be redistributed to DNs A (*S. José*) and B (*Sta. Maria*), and blood units returned from DN B (*Sta. Maria*) can only be redistributed to DN A (*S. José*).

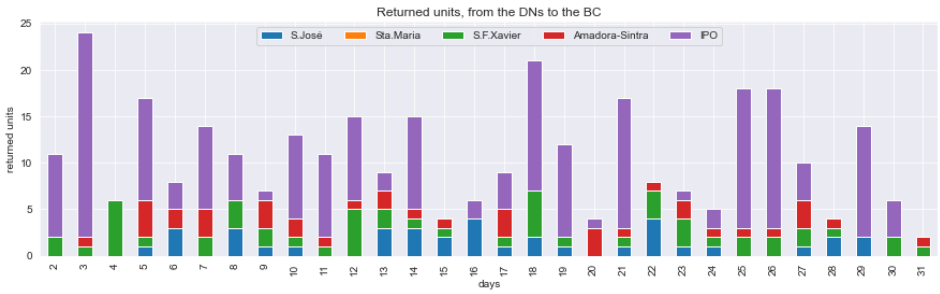

Figure 20 – Returned units, from the DNs to the BC, for model 1.

The number of returned units directly influences two costs – fuel and refrigeration. As it is clear from table 23, refrigeration costs for model 1 are higher, 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. From analyses on the returned units, as presented in figure 21, the latter is clear since more units are transported, contrarily to model 2, which only transports units from the BC to the DNs and comes back with no load. Hence, refrigeration costs in transportation are higher for model 1. 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:**

As presented in table 23, 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 (Meneses, 2019). Figures 21 and 22 present the substitution levels for both models, for transfusions at the DNs and for (re)distributions from the BC to the DNs.

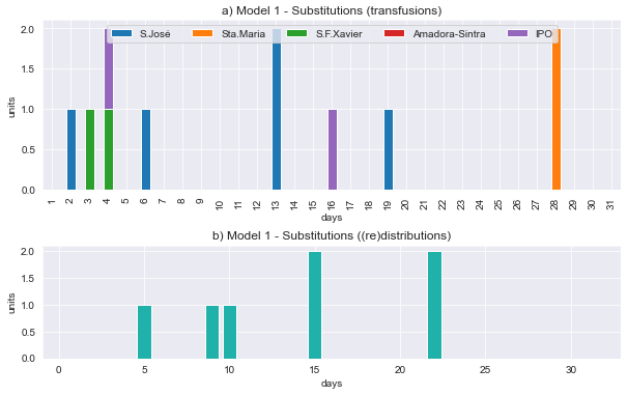

Figure 21 – Substitution levels for model 1: a) for transfusions at the DNs, and b) for (re)distributions from the BC to the DNs.

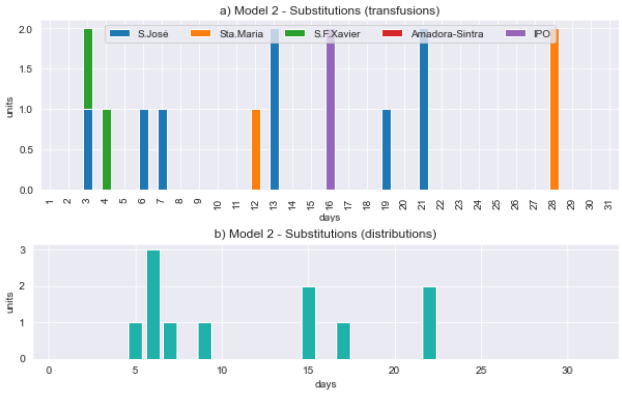

Figure 22 – Substitution levels for model 2: a) for transfusions at the DNs, and b) for distributions from the BC to the DNs.

- **Shortage levels:**

For both models, there are 9 units in shortage at the 3rd day of the month, at DN E (IPO). Hence, there is no conclusion to be taken on this topic for the redistribution and return of blood units, since, in this case, it does not bring any benefit related to shortage. However, these shortage levels are influenced by how the ordered quantities by the DNs are calculated, which in this model is as described with equation 26 - each period's orders quantities of each blood product and blood type are established by the demanded quantity at the same period, minus the still available inventory for the next period, plus the number of safety stock units used, to restore the safety stock at the DNs. Tus, 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, which results in shortage. This is exactly what happens at DN E (IPO), which has no demand until the third day, and which has a maximum age of 2 days. Since its minimum inventory levels are never reached at the first and second days and there is no demand, then there are no orders at the first two days and, at the third day, the inventory is empty. Hence, at the third day, when there is demand, there is no inventory available to meet demand, resulting in total shortage. So, these shortage levels are the result of the model's limitation in calculating the ordered quantities by the DNs. 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:**

According to the costs associated with refrigeration, which are costlier for model 1, 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. The latter is expected, since, as mentioned previously, for this model, besides the units transported from the BC to the DNs, more units are transported back to the BC, increasing the costs of refrigeration during transportation.

Concerning the units in storage, the results on the daily inventory levels 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, as presented in figure 23 which displays the daily inventory at the BC, per age of the units, for both models. This complies with the costs and with what was 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, figure 23 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.

Figure 23 – Total daily inventory levels at the BC, per age of units, for a) model 1 and b) model 2.

- **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. Figure 24 displays the average ages at transfusions for each DN and for each model. As expected, for model 1 the average ages are the same or higher than for model 2, due to the possible blood reutilization.

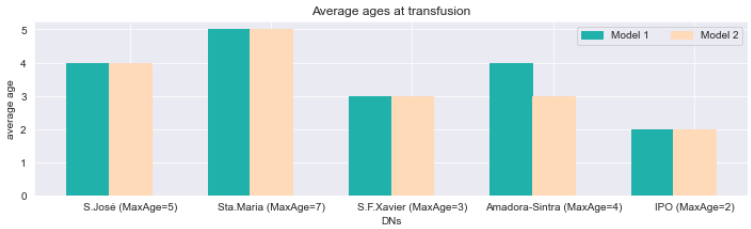

Figure 24 – Average ages for each DN and for each model, at transfusions.

6.4. Sensitivity analysis

The results presented in section 6.3. are condensed into figures 25 and 26, which show how the models dealt with the total units of the month (the initial inventory in the DNs plus the total supply for the whole month plus the shortage): wasted units (at the BC and at the DNs), transfused units (normal or in substitution), shortage units and units kept in inventory at the last day of the month (at the BC and at the DNs).

Overall, there is a very small difference between the total wastage levels of the two models tested, of 0,5%. Yet, the goal was to minimize wastage, which, even if only for 9 units, was accomplished. Also, as mentioned throughout this dissertation, blood is essential and any waste of units should be prevented.

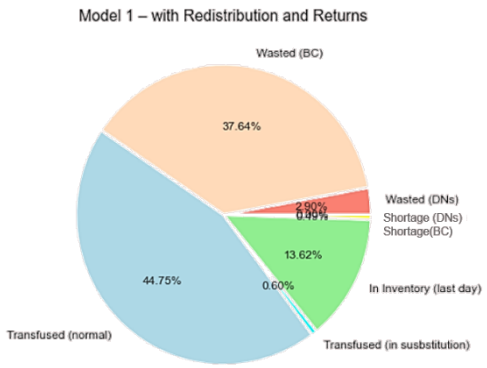

Figure 25 – Results on wastage, transfusion, shortage and remaining inventory, for model 1.

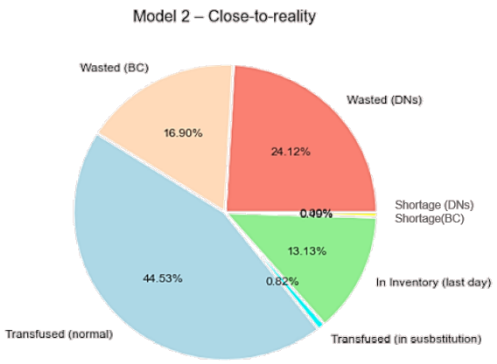

Figure 26 – Results on wastage, transfusion, shortage and remaining inventory, for model 2.

However, the observed small difference in wastage between the two models can be influenced by other factors, such as the levels of demand, which, if higher and more frequent, could prevent the wastage of units at the BC after being returned from the DNs, or the short SL of the considered blood product, which is the lowest SL of the other possible blood products, as presented in table 9 from chapter 3. The shorter the SL, the less time to manage and reuse units in inventory. For instance, in case of RBCs, which have a SL of 42 days, a maximum age of, for example, 30 days, enables the units to be kept in inventory at the BC for a longer time until being redistributed. Hence, a sensitivity analysis is 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 equal to the new SL. For this analysis, model 1 was run for 4001 seconds (about 1 hour and 10 min), and presented a feasible solution with a gap of 6,3%, and model 2 was run for 3601 seconds (about 1 hour), and presented a feasible solution with a gap of 7,3%. Table 24 presents the results from section 6.3., with a SL of 7 days, and the from this sensitivity analysis, with a SL of 15 days, for both models, regarding the wasted units, transfusions, substitutions, average age of the daily inventory and average age of transfused units.

Table 24 – SL = 7 days vs. SL = 15 days: comparison in cost, wastage, transfusions, substitutions, average age of daily inventory at the BC and average age of transfused units at the DNs.

		SL = 7 days		**SL = 15 days**	
		Model 1	**Model 2**	**Model 1**	**Model 2**
Wasted units (DNs)		53	441	12	343
Wasted units (BC)		688	309	398	112
Total wasted units		741	750	410	455
Transfused units (normal)		818	814	793	810
Transfused units (in substitution)		11	15	36	19
Substitutions in (re)distribution		7	11	12	32
Average age of units in inventory (BC)		4 days	3 days	6 days	5 days
Average age of transfused units (DNs)	A (*S. José*)	4 days	4 days	4 days	4 days
	B (*Sta. Maria*)	5 days	5 days	8 days	9 days
	C (*S. F. Xavier*)	3 days	3 days	3 days	3 days
	D (*Amadora-Sintra*)	4 days	3 days	4 days	4 days
	E (IPO)	2 days	2 days	2 days	2 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, as described is subsection 3.5.4., even if performing substitutions can be perceived as poor quality service, as argued by Katsaliaki (2008), it provides more flexibility and prevents unnecessary outdated units, as concluded by Duan & Liao (2014) and as it is clear by these experiments, which show that model 1 is beneficial in terms of wastage.

Figures 27 and 28, similarly to figures 25 and 26, show how model 1 and model 2, respectively, 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 (21,77% at the BC and 0,66% at the DNs), whereas for model 2, 25,0.% of total units were wasted (6,16% at the BC and 18,86% at the DNs). 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%).

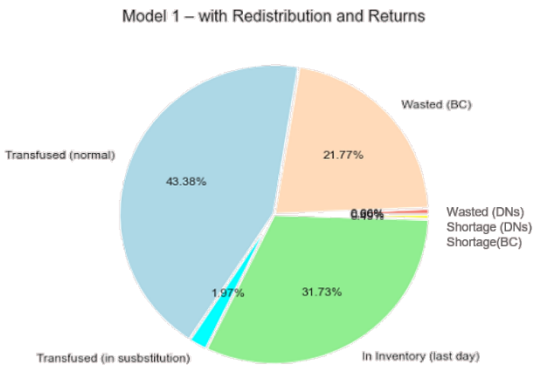

Figure 27 – Results on wastage, transfusion, shortage and remaining inventory, for model 1, for a SL of 15 days.

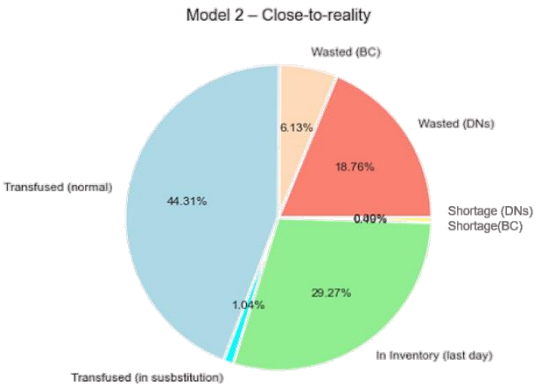

Figure 28 – Results on wastage, transfusion, shortage and remaining inventory, for model 2, for a SL of 15 days.

6.5. Main chapter conclusions

The innovative BSC model formulated in chapter 5 was applied in chapter 6 for the Portuguese case, particularly for 5 DNs of the LVT region, using data from 2019 for pools of PLTs with PR.

At first, section 6.1. presented all the data and assumptions made to test the model, including the supply and demand from December of 2019 provided by an IPST source, all the related costs with inventory management and

(re)distribution, as well as the maximum ages assumed for each considered DN and their driving distances and times to the BC.

Then, section 6.2 presented the KPIs to be analyzed with the results, namely: total costs, waste levels, levels of returned non-fresh units, shortage levels, substitution levels, daily inventory levels and the age of transfused units.

Later, section 6.3. presented the results from the computational experiments of the optimization model. The formulated model was also additionally tested without the group of parameters, constraints and calculations on the redistribution and returning of blood products, to compare the two formulations and conclude if the redistribution and returning of blood units to the BC is in fact useful to avoid wastage of blood, which is the main goal of the innovative BSC model from this dissertation. The results for the costs suggested that the non-consideration of redistribution and returning of blood results in more wastage and in more blood type substitutions, and that the inventory at the DNs falls below the minimum level more often. Additionally, the costs for refrigeration were greater with the consideration of redistribution and returning of blood, which came in line with the higher levels of inventory in this case, due to the returned units from the DNs. As for wastage, although in only 9 units, the results showed its minimization, and as for the age of the transfused units, the restriction to each DN's maximum age clearly resulted in a better quality service as blood transfusions occurred with fresher units.

The difference in the total wastage levels for the two formulations tested was of only 0,5 %, in terms of the totality of units handled during the whole month (total supply, final inventory and shortage units). However, this small difference can be influenced by the short SL of the PLTs. Hence, a sensitivity analyses focused on the SL of the managed blood product was performed in section 6.4., to understand if the consideration of a blood product with a greater SL contributes to less waste by increasing the chances of the returned units being used, since this way the units can be kept in inventory for longer until being redistributed. As it was intended, the results for a SL of 15 days (for which the DNs maintained the same maximum age except for DN B whose maximum age equals the SL), showed a greater minimization of wastage, as model 1 prevented the waste of 45 units when compared to model 2, which means a decrease in 2,48% in total wastage for model 1, higher than with a SL of 7 days.

Therefore, it is concluded that the formulated model is beneficial in reducing the wastage of blood. Although the differences are relatively modest, any waste should be avoided, and this model has proved that it is possible to do so. However, as the sensitivity analysis demonstrated, products with higher SL benefit even more from the consideration of the redistribution of blood.

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, throughout this work the importance of blood and the challenges faced by the BSC management highlight the importance of optimal and beneficial BSC management, making this a topic worthy of investigation to best ensure the availability of blood and blood products, while keeping waste levels to a minimum.

Firstly, a case study for the Portuguese context was developed, characterizing IPST, the entity responsible for all blood-related activities in Portugal, which works as a centralized system with three regional BCs – CSTP, CSTC and CSTL, that together cover all the country's mainland territory –, and which has 4 main stages – collection, processing and testing, inventory and distribution. After analyses of collection and transfusion data, it is concluded that the Portuguese system presents some inefficiencies that compromise the optimal functioning of the BSC, such as asymmetries in donations by region and by hospital blood units, imbalances between supply and demand, an inefficient regional distribution of the BCs and high levels of wastage, particularly for PLTs. Thus, the identified problems for the Portuguese case add the importance to the development of an efficient and sustainable method to fix the inefficiencies raised.

Hence, the stages, features, decisions, challenges and inefficiencies described for the Portuguese case were further supported by a literature review on BSCs, namely from the reviews by Torrado & Barbosa-Póvoa (2022), Meneses et al. (2022) and Pirabán et al. (2019), from which it was also identified what has already been performed in literature towards addressing the existing problems of the BSC. The BSC network can either be a centralized, as in Portugal, or a decentralized system, and it is generally divided into 4 stages − collection, production, inventory and distribution. Most research focuses on problems from single stages, yet it is clear that a more integrative view of the BSC stages is missing, considering all the entities and processes in the BSC and interrelations between them. Nevertheless, inventory is the most addressed stage in the literature, while production presents the less research. The most addressed objectives for BSC from the literature are the minimization of the total costs and the minimization of the wastage and shortage levels.

Additionally, a literature review on other perishable SCs was also performed, particularly the AFSC, in order to find possible transfers of knowledge from the AFSC to be applied in the BSC. 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, some modelling insights from this SC 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 (whose SL is of 7 days), which, according to the Portuguese case study, have been the most wasted blood product in the BSC throughout the previous years. The goal was to minimize wastage, as well as the total costs, substitutions, shortage and the average ages of the transfused blood units.

Computational experiments were performed for 2 models: firstly the formulated one, and then without considering the returning and redistribution of blood. 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, are used for

transfusions. Also, the main goal was accomplished since there was wastage minimization, even if in modest quantities, when considering the model developed with redistribution and returning of blood. 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, such as WB or RBCs, with SLs of 35 and 42 days, respectively, 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. Additionally, other further suggestions 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;
- → 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.

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