Optimal configuration and planning of a blood supply chain network under an uncertain environment

Sandrina Pereira Francisco

Dissertation to obtain the Master of Science Degree in

Industrial Engineering and Management

Supervisors: Prof. Ana Paula Ferreira Dias Barbosa Póvoa
Prof. Daniel Rebelo dos Santos

Examination Committee

Chairperson: Prof. Tânia Rodrigues Pereira Ramos
Supervisor: Prof. Ana Paula Ferreira Dias Barbosa Póvoa
Members of the committee: Prof. Ana Cristina Dos Santos Amaro

November 2021

Acknowledgements

To my supervisors, Professor Ana Póvoa and Professor Daniel Santos, for their guidance and dedication to this dissertation, for the knowledge transmitted on the topic and for the recommendations in the most challenging decisions. Also, to Odete, for her tireless availability throughout the last year.

To my maternal grandparents, for their constant loving and caring presence throughout my life, not always graced with due time and attention.

To my parents, for all the efforts they made so that I could follow the path I aspired to without any worries and for never doubting me.

To my brother, for his example in Engineering, for his advice and for being my confidant in the most difficult moments.

To the friends who accompanied my academic journey, with whom I had the privilege of sharing many long nights of study, but also moments of laughter, for their support and companionship.

Thank you!

Abstract

Blood products are indispensable to life. Besides, they are perishable and there are no substitutes. Supply depends on voluntary donations and is therefore irregular over time, and demand is stochastic, depending in part on unpredictable events. Given the vital nature of blood products, shortage scenarios are not acceptable and wastage is also ethically reprehensible since human blood is obtained through the solidarity of donors. It follows, then, that the management of the blood supply chain is complex.

The aim of this study is to understand how the blood supply chain has been studied and how is possible to contribute to the optimal design of such system considering uncertainty. Thus, a comprehensive tactical-strategic optimisation model is developed that allows studying the optimal planning and location of blood facilities. The model addresses uncertainty by means of two-stage stochastic programming and minimises operational costs inherent to supply chain operation, wastage, shortages, substitutability and carbon emissions.

In addition, a case study of the Portuguese blood supply chain is presented. The panorama of activity in the blood domain in Portugal reveals wastage and a recurrent imbalance between demand and supply. The model developed is applied to the particular case of the Lisboa e Vale do Tejo region considering the deterministic and stochastic developed approaches. It is concluded that the stochastic approach presents lower wastage, compared to the deterministic one, but higher shortage and, consequently, lower service level.

Keywords: Blood Supply Chain; Network Design; Perishability; Two-Stage Stochastic Programming; Uncertainty.

Resumo

Os produtos sanguíneos são imprescindíveis à vida. Acresce que são perecíveis e não existem substitutos. A oferta depende de dádivas voluntárias, logo é irregular ao longo do tempo, e a procura é estocástica, dependendo, em parte, de eventos imprevisíveis. Dado o caráter vital dos produtos sanguíneos, não são aceitáveis cenários de escassez e o desperdício é também eticamente reprovável, visto tratar-se de sangue humano obtido através da solidariedade dos dadores. Depreende-se, então, que a gestão da cadeia de abastecimento do sangue é complexa.

O objetivo do presente trabalho é compreender a cadeia de abastecimento do sangue e como é possível contribuir no sentido de otimizar a sua configuração, considerando a incerteza. Deste modo, é desenvolvido um modelo de otimização tático-estratégico abrangente que permite estudar o planeamento e localização ótima das instalações de sangue. O modelo aborda a incerteza através da programação estocástica em duas fases e minimiza custos operacionais inerentes ao funcionamento da cadeia de abastecimento, o desperdício, a escassez, a substituibilidade e as emissões de carbono.

Ademais, apresenta-se o caso de estudo da cadeia de abastecimento do sangue Portuguesa. O panorama da atividade no domínio do sangue em Portugal revela desperdícios e um desequilíbrio recorrente entre procura e oferta. Assim, o modelo desenvolvido é aplicado ao caso particular da região de Lisboa e Vale do Tejo considerando as abordagens determinística e estocástica desenvolvidas. Conclui-se que a abordagem estocástica apresenta menor desperdício, em comparação com a determinística, mas maior escassez e, consequentemente, menor nível de serviço.

Palavras-chave: Cadeia de Abastecimento do Sangue; Incerteza; Perecibilidade; Programação Estocástica em Duas Fases; Projeto de Rede.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BSC – Blood Supply Chain

CST – Centro de Sangue e da Transplantação

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

IPST – Instituto Português do Sangue e da Transplantação, IP

PLT – Platelet

RBC – Red Blood Cell

Rh – Rhesus factor

SC – Supply Chain

SCM – Supply Chain Management

SCND – Supply Chain Network Design

WB – Whole Blood

1. Introduction

This chapter aims to introduce the problem to be addressed in this dissertation and is divided into three sections. Section 1.1. presents the contextualisation and motivation of the problem. In Section 1.2. the objectives of the work are listed and explained. Finally, Section 1.3. presents the structure of the dissertation, namely the chapters in which it is organised, and briefly describes what each one presents.

1.1. Contextualisation of the problem and motivation

For several centuries blood was seen as a mystical fluid that fascinated ancient peoples. Although they did not know its composition and biological functions, they were aware of its vital nature. Several experiments were performed with blood, both animal and human, in an attempt to answer people's curiosity (The New Yorker, 2021). Among these are transfusions – operations by which blood or specific blood components from one organism are passed into the circulatory system of another.

It was in the 17th century that the study of blood began to acquire scientific foundation, in particular with the discovery of the circulatory system and its functioning. In 1628 William Harvey documented that the heart pumps blood throughout the body from the arteries and that it returns to the heart through the veins. From then on, experiments with blood multiplied all over the world. The first successful blood transfusion took place in 1818, following a childbirth in which a woman received blood from her husband. However, much remained undiscovered. Blood often clotted, making transfusion impossible, and severe reactions occurred in transfused patients, resulting in many deaths. It was in 1900 that Karl Landsteiner took one of the most important steps in blood research by discovering the existence of three blood types – A, B and O. He found that sometimes, when mixing blood from two individuals, certain blood cells would clump together, and deduced that the bloods were incompatible. Two years later, the scientist and two of his students discovered another blood type – AB. The ABO system was thus discovered. Since then, various anticoagulant solutions, i.e., compounds that prevent or reduce blood clotting, have been introduced, but it was not until 1939 that another essential blood system was discovered. Philip Levine and R. E. Stetson documented the existence of a factor that explained the occurrence of severe reactions in patients transfused with blood of their blood type according to the ABO system (National Blood Transfusion Service, 2020). This factor, which is a protein, was later called the Rhesus factor (Rh) and, depending on its presence or absence, gives rise to two types of blood – Rh positive (+) or Rh negative (–), respectively. This concluded the discovery of the most commonly used blood classification, ABO/Rh, that results in eight blood types: A+, A–, B+, B–, AB+, AB–, O+ and O– (American Red Cross, 2021a). Research in the field intensified, but it was not until the second half of the 20th century that the practice of blood collection and transfusion became widespread in the world (IPST, 2020).

It is now known that blood plays a very important role in breathing, nutrition, regulation and defence of the human body. It is made up of blood cells, such as red blood cells (RBCs), white blood cells and platelets (PLTs), immersed in a liquid called plasma, in which proteins and other compounds circulate in trace amounts. Plasma represents 55% of the total blood volume, RBCs represent 44%, and PLTs and white blood cells represent less than 1% (Etablissement Français du Sang, 2021). The various blood components have distinct morphologies and it is the molecules they present on the surface that

determine the blood type. The ABO system classifies blood according to the presence or absence of antigens on the RBCs. Antigens are molecules that cause the formation of specific antibodies to fight molecules that are foreign to the human body. Thus, antigens have the ability to trigger defence mechanisms of the immune system (American Red Cross, 2021a). An individual whose blood type is A has A antigens on the surface of RBCs and anti-B antibodies in the plasma, and an individual whose blood type is O has neither A nor B antigens, but anti-A and anti-B antibodies. When a patient is transfused with blood incompatible with his own, the recipient's antibodies and the donor's antigens clump together and the RBCs are destroyed, which can lead to death (Etablissement Français du Sang, 2021). Thus, it is important to know the complementary ABO and Rh systems to assess the compatibility between donor and recipient before transfusion.

Table 1 shows the possible substitutions between donors and recipients in the case of RBC transfusions. Each row indicates to which individuals each donor can donate RBCs, and each column indicates which type of RBCs each patient can receive. O– individuals are said to be universal donors because their RBCs can be transfused to any patient. In addition, this is the most sought-after blood type in emergency situations where the patient's blood type is unknown and a WB transfusion is required. O+ individuals can donate RBCs to any Rh (+) patient. Thus, this blood type is also very sought-after, as it is estimated that 80% of the population can receive it. In contrast, AB+ individuals are called universal recipients, as they can receive RBCs from anyone else. (American Red Cross, 2021a).

Table 1 - RBC compatibility matrix according to the ABO and Rh systems (adapted from Duan & Liao (2014))

Donor	Recipient							
	O+	O–	A+	A–	B+	B–	AB+	AB–
O–	✓	✓	✓	✓	✓	✓	✓	✓
O+	✓		✓		✓		✓	
A–			✓	✓			✓	✓
A+			✓				✓	
B–					✓	✓	✓	✓
B+					✓		✓	
AB–							✓	✓
AB+							✓	

There are numerous clinical situations that motivate a blood transfusion as therapy, and these play a very important role in medical care today. However, despite scientific and technological progress in recent decades, significant disparities still exist between developed and developing countries, especially with regard to donations, the therapeutic application of transfusions and access to blood products. According to the World Health Organization (2021), 40% of the world's total donations are collected in developed countries, home to only 16% of the world's population. Specifically, the donation rate in developing countries is only 5 donations per 1,000 inhabitants, which compares to 31.5 donations per 1,000 inhabitants in developed countries. In the latter, blood products are mainly intended to improve the quality of life of the population over 60, who receives about 75% of transfusions. These are used to support advanced medical procedures such as surgery or cancer treatments. In developing countries, more than half of all transfusions go to children under 5. In addition, the blood products administrated differ in both situations.

Blood products are defined as whole blood (WB), i.e., blood in its unaltered state after collection in anticoagulant solution, and WB-derived products. The most common WB-derived products are RBC and

PLT concentrates, plasma and cryoprecipitated antihemophilic factor, also called cryo. These are obtained by processing WB to separate it into specific blood components. It is usually much more effective to transfuse specific components as they perform different functions and are therefore not all equally suited to different pathologies. Table 2 shows the main characteristics of each one of these blood products.

Table 2 - Characteristics of blood products. Source: American Red Cross (2021b); Australian Red Cross (2020)

Blood product	Shelf life	Storage conditions	Key uses in medicine
WB	Up to 35 days[1]	Refrigerated (2 – 6ºC)	Trauma, surgery
RBCs	Up to 42 days[1]	Refrigerated (2 – 6ºC)	Trauma, surgery, anaemia, any blood loss, blood disorders
PLTs	5 days	Refrigerated (20 – 24ºC)[2]	Cancer treatments, organ transplants, surgery
Plasma	1 year	Frozen (at or below -25ºC)	Burn patients, bleeding disorders
Cryo	1 year	Frozen (at or below -25ºC)	Haemophilia, Von Willebrand disease[3]

Only 37% of WB donations are separated into components in developing countries, while 97% are separated in developed countries (World Health Organization, 2021). Indeed, separation into blood components requires dedicated equipment and facilities, which in countries with limited resources is not always possible.

The establishment of several blood facilities, constituent parts of the blood supply chain (BSC), is essential to ensure the collection, production, storage and distribution of safe, effective and quality blood products. It was in 1926 that the first blood transfusion service was established in England (National Blood Transfusion Service, 2020). Since then, BSCs have evolved with increasingly specialised facilities. These ensure that all processes essential to the provision of blood products are performed and are therefore key resources in any healthcare system. The World Health Organization (2021) recommends that blood facilities should be coordinated at a national level, establishing integrated networks of blood supply. For these blood facilities to fulfil their primary mission, which is matching supply with demand, it is essential that they are strategically designed.

Supply chain network design (SCND) consists of planning the physical location and capacity of facilities and aims to find the most efficient network configuration. To do so, it must consider several parameters, such as costs and distances, and the particularities of the products. Blood is a perishable product, i.e., it has a very limited shelf life after which it must be discarded (Nagurney et al., 2012). There is also a wide range of blood types and products, all of which require specific storage and transport conditions. Moreover, no blood product has substitutes and their availability often depends solely on the solidarity of voluntary unpaid donors (World Health Organization, 2010). Thus, it follows that supply is fairly irregular over time, constituting a source of uncertainty, alongside demand, which is also stochastic (Nagurney et al., 2012). As blood products are vital, it is not acceptable that they are not available when needed, but their wastage is also reprehensible. All these factors make the design of BSC networks highly complex and research-worthy.

[1] Depending on the type of anticoagulant that is added to it
[2] With constant agitation
[3] Specific blood clotting disorders

According to the Organisation for Economic Co-operation and Development (2019), 21% of the Portuguese population is aged over 65 and the average life expectancy in the country has been increasing since 2000, standing at 81.6 years in 2017, a figure higher than the European average. These data suggest that in the future there will be a greater demand for healthcare in Portugal, which implies a greater demand for blood products. Thus, it is essential to have a robust BSC in the face of uncertainty, both in demand and supply, that ensures the population's access to blood products. To this end, blood facilities must be strategically located so that there is no shortage in certain places and wastage due to outdating in others.

The aim of this work is to develop a mathematical optimisation model within the scope of BSC network design under supply and demand uncertainty, given the literature to date. In other words, the purpose is to develop a comprehensive tactical-strategic model that represents an in-depth contribution to the literature. The model is to be applied in the Portuguese context as a case study, since the literature on the BSC in Portugal, particularly on the configuration of the network, is scarce.

1.2. Dissertation objectives

The main objective of this dissertation is to develop a generic mathematical optimisation model aimed at designing and planning a BSC network. The model is expected to constitute a decision support tool on which are the most appropriate locations to install and plan blood collection facilities. Furthermore, it should ensure that demand is met at the lowest possible cost and wastage, maximising the service level. The developed model is then to apply to the Portuguese BSC allowing to analyse its structure and possible optimisation. Thus, the objectives of the dissertation are:

1) To conduct a literature review on BSC management and network design under uncertainty, characterising the whole problem and the existing methods of approach;
2) To formulate a generic mathematical optimisation model that addresses the main problems identified in the management of a BSC, so as to optimise it. The model should simultaneously contribute to the existing literature on network design under uncertainty in that it is more comprehensive;
3) To present the organisation and functioning of the BSC network in Portugal, identify the factors at the origin of the decisions affecting its current configuration and the main inefficiencies;
4) To apply the developed model to the Portuguese BSC, critically analyse the results and identify a possible set of improvements.

1.3. Dissertation structure

The dissertation is structured into seven chapters, all of which begin with a description of how they are organised and the content presented. Additionally, all chapters close with a concluding section in which the topics to be retained are summarised. The seven chapters are outlined as follows:

- **Chapter 1 – Introduction**
  It consists of this chapter, which introduces the problem to be addressed by means of a brief historical contextualisation and motivation. It also includes the presentation of the objectives and structure of the work.
- **Chapter 2 – Literature Review: Characterisation of the blood supply chain and supply chain network design and planning under uncertainty**
  The BSC and the state-of-the-art in SCND under uncertainty are characterised supported by a literature review. The configuration of centralised BSC network, its organisation and activity is described, the latter being organised by echelons. Also, approaches to uncertainty in the context of SCND are explained, with emphasis on the work developed in the blood domain.
- **Chapter 3 – Problem statement and model formulation**
  In this chapter the problem is described in detail, the decisions to be taken and the assumptions made are listed, and the performance measures to be applied in the analysis of the model results are set out. Also, the mathematical formulation of the generic model developed to address the problem is presented.
- **Chapter 4 – Case Study: Instituto Português do Sangue e da Transplantação, IP**
  The Instituto Português do Sangue e da Transplantação, IP (IPST), which regulates the BSC activity in Portugal, its functioning and the blood scene in Portugal is presented. In addition, the case study chapter identifies the main inefficiencies of the aforesaid supply chain.
- **Chapter 5 – Data collection and treatment for the Portugal Case Study**
  In this chapter the data required to implement the model is summarised. Specifically, the constitution of the model sets is defined and the values adopted for the parameters are presented. The extrapolations and assumptions made are also clarified.
- **Chapter 6 – Results and discussion**
  This is the chapter devoted to the presentation and discussion of the results. The deterministic approach of the model is first implemented and then the stochastic one, which targets the uncertainty in supply and demand. All results are critically analysed.
- **Chapter 7 – Conclusions and future research**
  It is the final chapter of the work, which summarises the key findings. It also includes managerial insights for the Portuguese BSC, based on the results obtained for the Lisboa e Vale do Tejo region, and proposals for future research on the topic of SCND under uncertainty.

2. Literature review: Characterisation of the blood supply chain and supply chain network design and planning under uncertainty

This chapter aims to review the existing literature on the BSC and SCND problems under uncertainty. In Section 2.1. the supply chain and supply chain management concepts are presented. This is followed by Section 2.2., which is divided into three subsections where the BSC is detailed. In Subsection 2.2.1. the notions of centralised and decentralised BSC and the typical centralised network configuration are presented. Then, in Subsection 2.2.2., the echelons of the BSC and their processes are introduced. After describing the constitution and functioning of the BSC, the key performance measures are presented in Subsection 2.2.3. Next, Section 2.3. proceeds with a review of the work developed on SCND, highlighting the main paradigms identified. In this context, as uncertainty is a key planning factor, Section 2.4. presents several approaches to the topic. Section 2.5. comprises a review of recent literature devoted to the design of blood supply networks. Finally, the chapter ends with Section 2.6., where the main conclusions, the identified gaps and what is the contribution of this work to the literature are outlined.

2.1. Supply chain and supply chain management

A supply chain (SC) consists of a set of facilities that transform raw materials into finished products and which, according to Barbosa-Póvoa (2014), is responsible for delivering them to consumers "in the right location with the right quantity and at the right time". These facilities are usually geographically dispersed and constitute a complex system called the SC network (Tordecilla et al., 2021). Also, SCs are often characterised by their constituent echelons, i.e., by a set of key processes that are essential to their functioning. To ensure good SC performance, all operations and associated flows – material, information and financial – must be planned, implemented and controlled in an integrated and coordinated manner. This process is called supply chain management (SCM) and aims to deliver value products to customers at the lowest possible cost and to meet their service level requirements (Govindan et al., 2017). SCM is an essential activity for the success of any organisation and comprises three hierarchical decision levels – strategic, tactical and operational (Eskandarpour et al., 2015). Strategic decisions include defining the number of each type of facility, the respective location and installed capacity, and are logically associated with long-term time horizons. At the tactical level, decisions are taken in the medium-term and focus on issues such as inventory coordination and transportation. The scheduling of production, the selection of modes of transport and the definition of vehicle routes, for example, are topics on which decisions are taken in the short term and therefore fit into operational planning (Muriel & Simchi-Levi, 2003).

2.2. Blood supply chain

The BSC manages the flow of blood products through all its processes, from donor collection to transfusion to patients, and its primary goal is to ensure those blood products are always available regardless of where and when they are required to be transfused. As such, shortage scenarios should

be avoided under any circumstances, as these may imply the postponement of scheduled surgeries and periodic treatments, leading to high costs, and even deaths. The fulfilment of this goal assumes that BSCs are self-sufficient in terms of national blood reserves, that is, that the total amount of blood collected meets or exceeds a certain target, determined based on historical demand data (Bruno et al., 2019; Pirabán et al., 2019). The World Health Organization (2020) estimates that a minimum average of 20 to 25 regular donors – people who donate blood at least twice a year – per 1,000 inhabitants is required to ensure an adequate supply of national blood supplies, although needs vary across countries; and that only 10% of people eligible to donate are blood donors. Moreover, wastage is not desirable either, as blood donors are a scarce asset and have to respect a certain period between two consecutive donations, besides the inherent costs in obtaining and supplying blood products, e.g. recruitment and selection of donors, collection, testing and processing of donations, and distribution of blood products (Beliën & Forcé, 2012). Thus, an efficient BSC must seek to meet demand while reducing wastage and minimising total costs (Osorio et al., 2015). Meeting demand and minimising costs are two conflicting objectives and, considering the perishable nature of blood and the uncertainty associated with both demand and supply, it is easily understood that managing the BSC is rather complex.

There are several reviews on the BSC, three of which stand out. Beliën & Forcé (2012) focus on the classification of existing work to date into eight categories – (1) type of blood product, (2) solution method, (3) hierarchical level, (4) type of problem, (5) type of approach, (6) exact versus heuristic, (7) performance measures, and (8) practical implementation/case studies. For each of these categories, the authors highlight the most important contributions, identify recent trends, and on which areas research should focus in the future. Specifically, the authors conclude that research to date (1) focuses on solving problems dedicated to specific blood types, namely RBC and PLT; (2) most frequently uses simulation as a quantitative approach to problems; (3) little explores problems integrating the entire BSC; (4) is far more extensive with respect to inventory and collection planning problems, than to distribution scheduling and supply-related problems; (5) privileges approaches that incorporate uncertainty over deterministic ones; (6) focuses almost equally on exact solution methods and heuristics; (7) does not prioritise quality and safety of blood products as performance measures; and (8) includes mostly practical case studies.

Osorio et al. (2015) develop their review on quantitative models in the BSC. The authors present these models into five categories. The first four focus on each of the four echelons of the BSC (illustrated in Figure 1) and the fifth category presents models that integrate all the echelons. For each category, a schematic representation of the decisions to be taken at each of the hierarchical levels is presented. The relationships between these decisions and the main gaps identified in each model category are also presented. The authors conclude that issues related to donor behaviour and inventory are often addressed, for example. Conversely, the allocation of donors to different collection methods lacks research. In addition, they point out that most literature focuses on only one echelon and thus there is a significant gap regarding models that integrate the entire BSC flow.

Figure 1 - BSC echelons, according to Osorio et al. (2015)

Recently, Pirabán et al. (2019) published a review that presents a classification that is different from the previous ones. According to this proposal, existing work is assigned to five categories – decision-making and forecasting environments, issues in the design of the BSC, processes and problems/planning decisions, modelling and solution methods, and data characteristics. Within the category 'issues in the design of the BSC', the analysis of the echelons of the BSC is highlighted. Five echelons are considered (illustrated in Figure 2), that contrast with those previously identified by Osorio et al. (2015). Specifically, the difference lies in the definition of echelon adopted. The present work employs a process-based definition, as does Osorio et al. (2015). However, Pirabán et al. (2019) adopts a facility-based definition, in which it considers that a set of facilities performing similar functions constitute an echelon (Govindan et al., 2017). Also in this review work by Pirabán et al. (2019), one of the main gaps identified relates to complex BSC configurations, i.e., configurations that consider several echelons and several facilities, and that study the interactions between them under an uncertain environment.

Figure 2 - BSC echelons, according to Pirabán et al. (2019)

2.2.1. Network configuration of the blood supply chain

In both literature and the real world, there are several different configurations for BSCs, but these can be reduced to decentralised and centralised systems (Beliën & Forcé, 2012; Osorio et al., 2015).

Decentralised systems are characterised by many dedicated blood facilities. Each of these facilities is independent, so they have the autonomy to govern themselves and decide on their operating policies. These systems are more common in developing countries and there are several reasons why they are adopted. In this regard, geographical remoteness is important, as it has a negative influence on the number of donations collected and increases the risk of stock disruption. Long distances between blood facilities and demand nodes are also relevant factors, resulting in higher transportation costs. Having a significant number of blood facilities mitigates these risks and is also socially beneficial as it contributes to regional economic development through the generation of employment opportunities (Osorio, Brailsford, Smith, et al., 2018).

Centralised systems, in turn, consist of several regional divisions, these having one or more blood facilities. Administration and authority over decision-making lie with top management that sets out the procedures to be followed by these facilities. Therefore, the blood facilities act in a coordinated manner and are interdependent. These systems predominate in developed countries and one of the main drivers of centralisation is economies of scale, allowing significant cost savings. In fact, the cost of a unit of a blood product that is processed in centralised systems can be up to 40% lower compared to the cost of that unit when processed in decentralised systems (Osorio, Brailsford, Smith, et al., 2018). In addition, centralised systems perform better in meeting the overall supply needs of demand nodes, present lower outdated rates, and lower overhead costs. Nevertheless, these systems require highly specialised labour to handle large quantities of blood products (Beliën & Forcé, 2012; Carden & DelliFraine, 2005; Osorio, Brailsford, Smith, et al., 2018). Figure 3 illustrates the network configuration of a centralised BSC. Centralised BSCs are the most complex and those requiring further research. Thus, decentralised

systems will not be addressed hereafter as they do not fall within the scope of this master's degree dissertation.

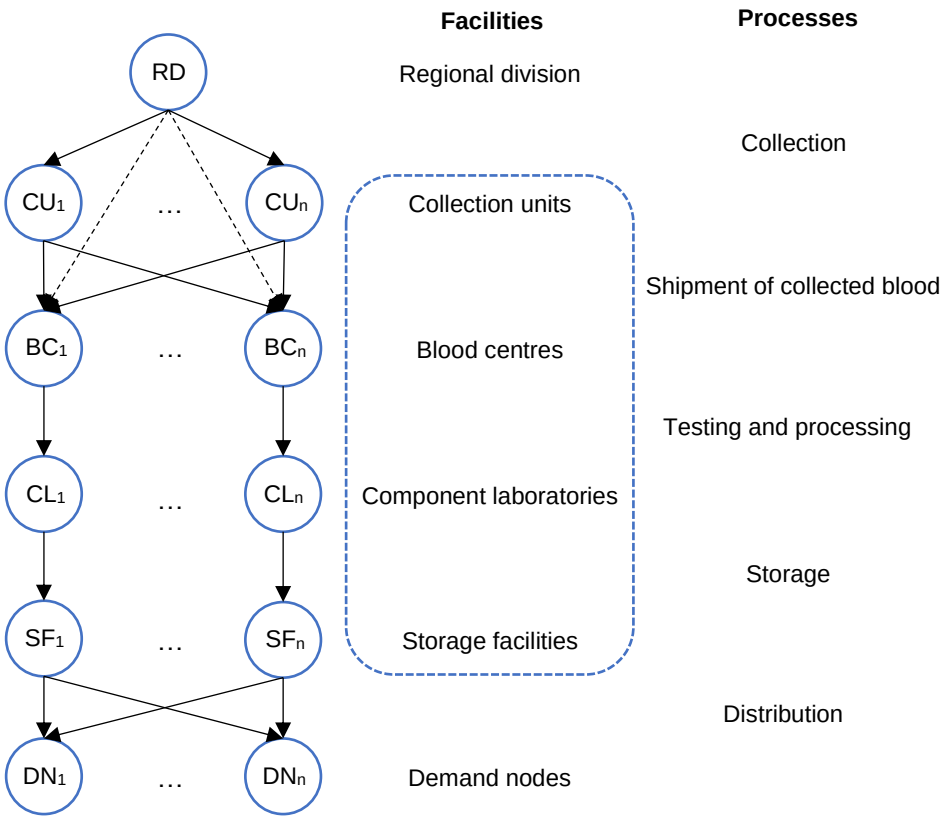

Figure 3 - Centralised BSC network configuration (adapted from Nagurney et al. (2012))

Each node represents a blood facility in the BSC network and each set of links between nodes at different levels represents a process. The top-level node represents a regional division and this is the entity responsible for planning blood collection sessions in the collection units represented at the second level. These facilities, denoted by CU_1, …, CU_n, may be of various types, as explained further in Subsection 2.2.2.1. Blood collection sessions may also take place in blood centres, identified by BC_1, …, BC_n, at the third level, therefore collection in these facilities is represented by dashed lines. It is to the blood centres that donations collected at the second level are sent, in a process known as shipment. Afterwards, they are tested and processed in component laboratories, denoted by CL_1, …, CL_n. The resulting blood products are then temporarily stored in storage facilities, represented at the fourth level by SF_1, …, SF_n, which are frequently in the same location as component laboratories. Subsequently, blood products are distributed to demand nodes at the fifth level, denoted by DN_1, …, DN_n, these being predominantly hospitals and surgical medical centres (Nagurney et al., 2012).

Several processes can be performed in the same location, as Figure 3 concerns a process-based network configuration rather than a location-based one. Testing, processing and storage are examples of these since both component laboratories and storage facilities are typically located within blood centres. Furthermore, blood centres can be equipped to operate as distribution centres (Nagurney et al., 2012). In fact, blood centres are the most common blood facilities and henceforth any reference to blood centres concerns facilities where collection, testing, processing, storage and distribution processes take place. There is also another process, called lateral transhipment, where blood products

are exchanged between blood centres or between demand nodes. This is a non-essential process and is not evidenced in Figure 3 for the sake of simplicity (Lee et al., 2007). In the following subsection, organised by echelons, all processes are detailed. The terminology adopted in this work meets that used by Osorio et al. (2015), so the echelons considered are collection, production, inventory and distribution.

2.2.2. Blood supply chain echelons

2.2.2.1. Collection

Collection is the first echelon in the BSC and aims to obtain the quantity of blood needed to satisfy the demand for blood products (Pirabán et al., 2019). The collection sessions consist of four phases. The first one encompasses receiving and identifying the donors. Thereafter, a clinical evaluation and physical exams are conducted, so that professionals can tell whether the donor can proceed with the donation or not. At this second phase, the donor's weight, height, blood pressure and haemoglobin concentration are measured. Blood collection takes place in the third phase and can be of two types – WB collection or apheresis. WB collection, in single, double, triple, or quadruple bags, is the most common type of blood donation and consists of a 450 *ml* blood withdrawal with the same composition as that circulating in the donor (Özener et al., 2019). Apheresis consists of the collection of isolated blood components and therefore requires specialised equipment that extracts only the desired components and returns the remaining blood to the donor. The collection of more than one isolated blood component is known as multi-component apheresis and the various desired components are collected into separate bags simultaneously. These blood components might be RBCs, plasma, or PLTs (Instituto Português de Oncologia do Porto Francisco Gentil, 2020). In the last phase of the collection session, donors receive a light meal during which they are supervised.

Collection sessions take place at specific locations, previously referred to as collection units and blood centres. Collection units include hospital blood units, mobile venues, and mobile vehicles. Hospital blood units are fixed facilities permanently equipped with the necessary material for donation, as are blood centres. Mobile venues refer to facilities that are not permanently equipped. Therefore, the necessary material has to be transported. Mobile vehicles are vans or caravans permanently equipped with the necessary material for blood collection that travel to various sites (DOMAINE, 2010). These vehicles are commonly referred to as bloodmobiles, a designation that will be adopted henceforth. Thus, collection at four different types of facilities are considered, which can be grouped into fixed collection sites and temporary collection sites. Blood centres and hospital blood units are included in fixed collection sites; mobile venues and bloodmobiles are included in temporary collection sites. The major difference between fixed and temporary collection sites concerns location, as temporary collection sites can be moved between several geographic points over the planning horizon, entailing an additional cost that depends on the geographical distribution of those points. Typically, the location of fixed collection sites is defined in the long term, so it cannot be changed during the planning horizon and the underlying decision falls within the strategic planning level (Gunpinar & Centeno, 2016; Zahiri et al., 2013). Besides location, fixed and temporary collection sites differ in capacity, functions, and costs. At fixed collection sites, blood donation is possible throughout the year and therefore most donations are collected in these sites. At temporary collection sites, donation sessions must be planned and scheduled in advance so

that they can be publicised. In addition to greater collection capacity, fixed collection sites also have more equipment, which implies higher establishment costs (Samani et al., 2019). With regard to functions, fixed collection sites are responsible for contacting donors to schedule collections and for setting the corresponding collection targets. In the case of bloodmobiles, it is the top management that decides on the appropriate number of vehicles to operate, when and in which locations. In particular, these locations must be public, e.g., governmental organisations, municipalities, colleges and certain events. For mobile venues, it is necessary to contact other entities, such as associations, ascertain the physical conditions of the facilities and agree on the schedule of collection sessions (Gunpinar & Centeno, 2016; Şahinyazan et al., 2015). Also, the allocation of human and physical resources to the temporary collection sites is in charge of top management, as a multidisciplinary team – secretaries, physicians and nurses – has to be assigned for each collection session in temporary collection sites (Pirabán et al., 2019). The preceding decisions, such as the planning of collection sessions and staff allocation, fall within the tactical planning level, while decisions on collection targets and staff schedules fall within the operational planning level, as these are taken considering medium and short-term time horizons, respectively (Osorio et al., 2015).

While fixed collection sites are usually equipped for both WB and apheresis collection, the same does not apply to temporary collection sites. In the case of collection sessions in mobile venues, only WB collection is possible. As for bloodmobiles, these can be single or double. Single bloodmobiles collect WB only, while double bloodmobiles are equipped to perform apheresis collections as well. WB donations collected in single bags will be later stored without being processed. The remainder will be processed into WB-derived products. WB collected in double bags yields RBC and PLT rich plasma, in triple bags yields RBC, plasma and PLTs, and in quadruple bags yields RBC, plasma and buffy coat, this is, PLTs and white blood cells (Pirabán et al., 2019). In addition to the blood products they generate, collection methods can be compared in terms of efficiency, frequency, duration, and cost. For example, to obtain a PLT transfusable unit, four to five units of WB are needed, whereas the collection of this blood component by apheresis allows to obtain up to three PLT transfusable units in just one session. Thus, it is evident that the yield of blood products by apheresis is considerably higher than that of WB collection, being the former one the most efficient method. Regarding the frequency of blood donation, it varies significantly across countries, even in Europe. In Portugal, for instance, men and women can donate WB up to four and three times a year, respectively, and the minimum time interval between donations is two months – deferral time (Özener et al., 2019; SNS24, 2020). However, in the case of apheresis PLT collection, the donor may make up to twenty-four donations per year; in the case of apheresis RBC collection, this is usually done in double doses and the donor may donate every six months; and in the case of apheresis plasma collection, this occurs only in specific situations (Instituto Português de Oncologia de Lisboa Francisco Gentil, 2020). As such, per year, it is possible to withdraw a greater amount of blood products from a donor when resorting to apheresis than when proceeding with a WB collection. In contrast, the cost associated with apheresis is higher, since it requires more expensive equipment, and it is a much more time-consuming procedure as it takes an average of 50 to 60 minutes (Instituto Português de Oncologia do Porto Francisco Gentil, 2020; Pirabán et al., 2019).

The duration of the bloodmobiles collection sessions is often addressed in the literature and there are several acting proposals. Şahinyazan et al. (2015) assume that bloodmobiles can park at certain locations for periods of two or three consecutive days, depending on the collection potential of each of these locations. Alternatively, Gunpinar & Centeno (2016) consider that collection sessions in bloodmobiles are planned for a period of three hours, although bloodmobiles can stay at that location for up to seven hours. Thereby, the number of locations that a bloodmobile can visit per day is limited.

As for the collection quantities, the existing literature is scarce. Lowalekar & Ravichandran (2010) consider that the quantity of blood to be collected can be restricted to reduce wastage stemming from eventual over-collection scenarios. In this regard, they develop a simulation model in order to assess and compare the performance of three collection policies in terms of shortage, wastage, and total costs. The first of these policies is the Unrestricted Collection, which is quite prevalent and consists of collecting blood from all donors. As the supply varies over time, this policy can result in great wastage in periods when collection levels are particularly high. The remaining two – Modified (Q, T) and Modified (R, T) – are cut-off level policies, in which the blood supply is restricted to a predetermined quantity. The former one consists of collecting a fixed quantity of blood Q, and the latter one of collecting a quantity that is equal to the difference between a target inventory level R and the stock level immediately before collection. Their conclusions demonstrate that both cut-off level policies outperform Unrestricted Collection in what concerns controlling total costs and wastage for a given level of shortages. However, the cut-off level must be carefully established to maintain a certain demand fill rate.

To conclude, the existing literature acknowledges that the collection process has inefficiencies that jeopardize the performance of the BSC. Williamson & Devine (2013) identify collection in mobile venues as one of those. Great emphasis is still placed on collection sessions taking place in mobile venues, in which both staff teams and physical collection resources have to travel, oftentimes over considerable distances, in order to carry out the collection. This situation is socially desirable, but the quantity collected does not always justify the costs incurred. Hence, it needs to be analysed if collection efforts should be concentrated on areas where people are most likely to donate. Also, the authors suggest that mobile collection locations should be reconsidered, as public sites do not always offer the best experience for the donor.

2.2.2.2. Production

After collection, the production echelon follows. This includes the testing and processing of blood components, which occur concurrently. Testing should ensure the quality, compatibility, and safety of blood and takes place at laboratories that are typically located within blood centres. Two types of tests are performed using only a small sample of the blood collections. First, the blood type of the donor is identified and then a battery of tests is conducted in order to inquire about the existence of transfusion-transmittable infections (Nagurney et al., 2012; Pirabán et al., 2019). The number of samples of blood collections tested and the range of tests carried out vary from country to country, although the World Health Organisation recommends the analysis of all blood donations for screening for transfusion-transmittable infections, including human immunodeficiency virus (HIV-1 and HIV-2), hepatitis B, hepatitis C and syphilis (Organização Mundial da Saúde, 2010). Besides these infections, if suspicions

of some disease arise during the clinical evaluation prior to blood collection, additional tests are performed (e.g., malaria). Multiple tests are available for the same infection, each with different effectiveness and cost. However, there are no fully reliable tests, as false-negative and false-positive results are possible (Bish et al., 2011). As such, a set of screening tests needs to be selected, so as to classify the blood donations as disease-free or infected (Pirabán et al., 2019). Bish et al. (2011) develop an analytical modelling and algorithmic approach to address this problem under resource-constrained environments and their conclusions highlight the importance of selecting region-specific screening tests, i.e., in accordance with the prevalence rate of certain infections in the region where blood donations were collected. Regardless of the results of the tests, blood samples are always discarded, and in case an infection is confirmed, the remainder of the corresponding blood donation is also discarded (Nagurney et al., 2012). Fragoulakis et al. (2014) appraise the production cost of one unit of blood from the perspective of the National Health Service in Greece. The study considers the resources expended in the collection, testing, processing and storage processes, and also the indirect cost of blood donations for donors, i.e., the inherent productivity loss. The authors conclude that the production cost of one unit of blood is not insignificant, as it is estimated at €131.49, and that the three major cost components are the cost of personnel, the nucleic acid testing and the cost of laboratory tests, accounting for 32.46%, 27.97% and 27.65%, respectively. In face of these results, it is important to stress that the two cost components associated with testing represent more than half of the total cost of producing a blood unit in Greece, which, from the cost point of view, emphasizes the relevance of this process in the BSC.

When blood collections arrive at processing centres, which are also typically located within blood centres, they are either stored, in the case of WB collections in single bags, or processed, in the case of WB collections in double, triple, or quadruple bags. Processing consists of using a centrifuge machine to separate blood components according to their density. This process is called fractionation and, depending on the speed and time of centrifugation, different blood products are obtained (Osorio, Brailsford, & Smith, 2018). In the case of apheresis collections, these are obviously not fractionated, but a donation gives rise to one or more transfusable units, depending on the blood component collected. This separation procedure is also part of the processing. Although fractionation allows only the desired blood products to be produced, i.e., it allows to adapt production to the needs of patients, it may not always be optimal to fractionate large amounts of WB, since the increased availability of blood products might also imply an increase in the costs of holding, processing and wastage in the blood centre (Beliën & Forcé, 2012; Lowalekar & Ravichandran, 2011). In this regard, Lowalekar & Ravichandran (2011) develop a simulation-based model to determine the optimal amount of WB to be fractionated in a blood centre, taking into account its objectives and context. Their work proves to be an important contribution to the management of blood centres, as it presents a tool that allows managers to test the impact that processing different amounts of WB has on the overall performance of the blood centre and make decisions accordingly. Besides, blood centre managers are also responsible for drawing up master production plans, allocating staff to activities and designing the layout of the facilities, which are tactical decisions. At the operational level, they are responsible for the daily planning decisions, such as scheduling the staff for testing and processing (Osorio et al., 2015). In what concerns testing and processing time, different assumptions exist in the literature. According to Wang & Ma (2015) and

Ensafian & Yaghoubi (2017), it takes two days for blood donations to be tested and processed into WB-derived products, but Katsaliaki et al. (2014), in contrast, assume that these processes take one day.

2.2.2.3. Inventory

The inventory echelon comprises the storage and inventory management processes. Storage consists of properly preserving blood products suitable for transfusion, i.e., according to the specific storage conditions of each one to safeguard its quality. It takes place at blood centres and hospital blood banks, these facilities being intended for pre-transfusion storage. Inventory management refers to a set of policies aimed at ensuring the availability of blood products in sufficient quantity and diversity to meet demand in any situation and in an efficient manner. In short, it aims at ensuring that all blood products for all ABO/Rh blood types are in inventory in sufficient quantity. After storage, the units in inventory at blood centres are either distributed, to other blood centres or to fulfil the orders placed by demand nodes, or discarded, when outdated.

According to Duan & Liao (2014) and Osorio et al. (2017), the most commonly used inventory review policy in blood centres is a 1-day period, meaning that the inventory state is updated every day. The 1-day period review policy is particularly advantageous as it allows for the coordination of inventory replenishment with distribution, which often occurs daily. As such, at the time of review, outdated units are removed for incineration, the residual shelf life of the remaining units is shortened by one day and newly received units are added. Since it is paramount to always keep an inventory of all types of blood products, blood centres should define a minimal safety stock for each product, which must be proportional to the variability of demand. Thus, for each day and each blood product, the maximum quantity that can be despatched is equal to the difference between the total inventory on hand and the safety stock – despatching rule (Osorio et al., 2017; Osorio, Brailsford, Smith, et al., 2018).

As per Osorio et al. (2017), demand nodes review their inventory level daily, following an order-up-to-level (R, S) policy. When the observed inventory level of a given blood product is lower than a certain value, a replenishment order is placed to increase the inventory back up to the S level. In the literature, other periodical inventory policies are frequently discussed. For instance, the old inventory ratio policy is an age-based policy that aims to improve the BSC performance. First, it determines the order quantity according to the order-up-to-level (R, S) policy, which considers only the total quantity of units in inventory, i.e., without safeguarding their residual shelf life. Then, the ratio between the number of old units in inventory and the total units on hand in that period is computed, with the old units corresponding to blood products whose residual shelf life expires in one, two or three days. If this ratio is greater than a given threshold, an additional order is placed to guard against possible wastage. The quantity requested in the additional order equals the total quantity of old units' inventory at the time of the review (Duan & Liao, 2014). Rajendran & Ravindran (2017) focus on demand node inventory ordering policies specifically designed to minimise wastage. In this sense, the authors present a stochastic integer programming model under demand uncertainty that aims to determine the number of PLT units that demand nodes should order and when to order. Also, they propose three ordering policies, namely (1) the modified order-up-to-level policy, which considers the coefficient of variation of demand and defines the desired inventory level, S', as a multiple of the average demand during the lead time and revision

period; (2) the weighted mean-variance policy, which considers the weighted average of demand and the standard deviation over several periods; and (3) the last value policy, where the quantity ordered at the end of the day is the sum of the demand observed on that day and the demand during the lead time and revision period. The performance of these policies is compared with each other and with the performance of the order-up-to-level (R, S) policy, considering several parameters. Among the most relevant findings is that if demand variability is low, then the most appropriate policy is (2); conversely, if demand variability is high, the authors recommend policy (1). Finally, in the case of demand nodes whose inventory storage capacity is low, policy (3) proved to be the most appropriate.

When the inventory review policy in place in demand nodes is a 1-day period, orders are sent to blood centres at the end of the day. These are oftentimes a combination of standing orders, i.e., orders aimed at replenishing the inventory depleted, and emergency orders to meet the demand for which there is no available inventory (Blake et al., 2013). The observation of demand is relevant because order quantities depend on target inventory levels, which are generally based on experience. Specifically, order quantities are given by the difference between target inventory levels and on-hand inventory (Abdulwahab & Wahab, 2014). It is common practice for blood centres to despatch orders overnight so that they are received by demand nodes early in the morning. Thus, it is reasonable to assume that the lead time is equal to zero – instantaneous replenishment (Blake et al., 2013).

There are two issuing policies frequently addressed in the literature – First In, First Out, in which the products despatched are those that have been stored the longest, and Last In, First Out, in which the products despatched are the ones that have been stored most recently (Pirabán et al., 2019). Abdulwahab & Wahab (2014) study hospital PLT banks and state that First In, First Out is the optimal issuing policy since it minimises shortages, outdated units, and average inventories. Also, it reduces the number of leap-frogged units, i.e., the number of fresher, non-expiring units when an older, expiring unit is available (Duan & Liao, 2014). At blood centres, orders are usually issued according to First In, First Out policy and processed in batches according to the average daily demand of the demand nodes served by the blood centre. Demand nodes with higher average daily demand receive blood products with lower residual shelf life, i.e., older units. In contrast, demand nodes with the lowest average daily demand receive newly stored blood products, which gives them more leverage for using the blood ordered without incurring wastage (Blake et al., 2013).

When the ordered blood products arrive at demand nodes, all units are classified as unassigned inventory, that is, they are not yet reserved for any patient. To test the compatibility between patients and blood products, pre-transfusion crossmatching tests are performed. The units assigned to patients are put aside and classified as assigned inventory. For instance, in many cases of scheduled surgeries, it is necessary, as a precaution, to have blood products assigned to patients – surgical reserves. However, these are not always transfused. When assigned units are left unused, they return to unassigned inventory, and the same applies to crossmatch-incompatible units (Duan & Liao, 2014; Pirabán et al., 2019). Units are also returned to the unassigned inventory after the crossmatch release period, which is the maximum time a blood product unit is stored in assigned inventory before it is returned (Osorio et al., 2015). The ratio between crossmatched units and units that are actually transfused is called crossmatch-to-transfusion ratio – C/T ratio (Pirabán et al., 2019). Perera et al. (2009)

analyse a set of blood inventory data from demand nodes and blood centres and assess how the crossmatch release period and the methods of calculating the blood product order quantity contribute to wastage. The authors conclude that 24-hour crossmatch release periods instead of 48 hours result in a higher probability of using the blood products, as they are less time reserved, and in lower inventory requirements. In addition to single crossmatching testing, there is a similar alternative procedure – double crossmatching testing – in which a blood unit is reserved for two patients while ensuring that if both patients need to be transfused, blood products are available for this purpose. This procedure aims to increase the likelihood that a unit in the assigned inventory will be used, meaning that there will be fewer unused assigned units that were not available to other needy patients (Beliën & Forcé, 2012).

Although both single and double crossmatching testing implies the existence of two types of inventories, the literature also presents a method for inventory management in demand nodes that relies on only one inventory - the Type & Screen procedure. The Type & Screen procedure, or electronic crossmatching, does not assign inventory to specific patients unless a transfusion candidate patient has any unexpected clinically significant antibodies. This means that the only blood inventory in demand nodes is the unassigned inventory. If a transfusion proves to be necessary, a blood unit is issued from the inventory available, and this unit must be compatible with the ABO/Rh blood group of the patient, which is known in advance (Duan & Liao, 2014; Pereira, 2005). In order to identify the factors that determine the efficiency of the Type & Screen procedure for surgical reserves, Pereira (2005) develop a simulation model that reproduces the blood product inventory operation at demand nodes. The author concludes that outdate and shortage rates grow exponentially with increasing variation in daily transfusions, being this the major factor influencing the performance of the inventory operation. Notwithstanding, this can be balanced with an increase in the residual shelf life of the blood products received from blood centres. As such, demand nodes with greater variation in daily transfusions should be supplied with fresher units.

To conclude, inventory management has been extensively studied in the literature over the years and most of the previous work is devoted to optimising the inventory of blood products in demand nodes, particularly the management of assigned inventory. The main findings are that the performance of blood inventories in demand nodes is optimised when blood products are issued according to the First In, First Out policy; the crossmatch-to-transfusion ratio must be very close to 1; and that the crossmatch release period should be as short as possible. These conclusions suggest that surgical reserves should be managed without constituting assigned inventory, which is possible when applying the Type & Screen procedure, instead of the pre-transfusion crossmatch compatibility testing (Pereira, 2005).

2.2.2.4. Distribution

Distribution refers to the movement of blood products between facilities in the BSC. It covers two processes – shipment and distribution to demand nodes.

Shipment is a BSC critical process that takes place immediately after collection. Vehicle fleets are used to transport blood collections from temporary collection sites to blood centres, as WB must be processed within six hours after collection – the processing time limit (Özener & Ekici, 2018; Pirabán et al., 2019). The processing time limit corresponds to the maximum time interval during which WB can

remain at room temperature conditions without compromising its quality. After this period, if the blood donation is not cooled, it may deteriorate due to bacterial contamination (Lowalekar & Ravichandran, 2011). In the literature, several authors dwelled on planning decisions in the shipment process. Şahinyazan et al. (2015) suggest the usage of motor vehicles, called shuttles, which would visit all bloodmobiles and transport the collected blood to the blood centres. Shuttles would also be able to provide the bloodmobiles with additional collection material resources when needed so that bloodmobiles would not have to return to the blood centre every day (Pirabán et al., 2019). Doerner et al. (2008) address a vehicle routing problem with multiple interdependent time windows for blood collections pickup. The minimum number of pickups for each collection location is calculated and time windows for all pickups are generated. Also, several operational research tools were developed to find the minimum cost routes and allocate the appropriate vehicles to those routes, minimising the total driving time. They conclude that increasing the number of pickups at selected collection locations beyond the theoretical minimum number of pickups has a great potential for cost reduction. Mobasher et al. (2015) propose a mixed-integer linear programming model and an algorithmic approach to coordinate pick up and appointment schedules at the temporary collection sites to maximise the PLT production. The goal of this study is to maximise the number of blood donations that can be collected and delivered to a blood centre for processing within the processing time limit. The authors assume that temporary collection sites are partitioned into clusters and that each vehicle is assigned to a single cluster. Thus, all temporary collection sites in a cluster are visited by the same vehicle. The model is a support tool for blood centre managers who have to schedule continuous pickups from collection units while ensuring that shipment is done within the processing time limit. With regard to the capacity of vehicles, Hemmelmayr et al. (2010) consider that the size of the blood bags is very small, when compared to the size of the vehicles, and therefore capacity is never restricting.

As regards distribution to demand nodes, blood products in demand are transported from the blood centres by vehicle fleets that must ensure timely delivery. In BSCs where regional divisions are made up of several blood centres, blood products may also be transported between facilities, whether these are blood centres or demand nodes, when there are shortages in one location and over-supply in another (Osorio et al., 2015). This is called lateral transhipment and refers to movements of inventory between similar facilities in the SC (Dehghani et al., 2021; Paterson et al., 2011). Its relevance in the BSC arises from challenges such as insufficient supply, limited shelf life, uncertain demand and supply, and high service level requirements (Wang & Ma, 2015). It is an operation that enhances the flexibility of the network, as it balances stock among facilities by reallocating inventory (Dehghani et al., 2021). These facilities can pool their inventories and thus reduce the safety stock levels, minimising inventory holding costs whilst maintaining the required service level (Paterson et al., 2011). Despite entailing an increase in distribution costs, lateral transhipment is widely recognised as being preferable to a non-transhipment policy (Lee et al., 2007). Two types of lateral transhipment exist – proactive and reactive transhipments – both of which allow the redistribution of stock between facilities. The former one occurs at predetermined moments in time, before demand is realised. The latter one occurs when an inventory shortage is realised and acts as a quick and effective solution to relieve the supply pressure of the demand nodes (Dehghani et al., 2021; Paterson et al., 2011). Lateral transhipment has been widely

addressed in the literature. Lee et al. (2007) propose a policy, called Service Level Adjustment, that combines reactive with proactive lateral transhipment and that relies on service level to decide on the quantity to be transhipped to meet demand. The authors focus on an item with high stockout cost, such as blood products, and conclude that the Service Level Adjustment policy has lower total costs and responds more effectively to changes in the demand than previous lateral transhipment policies. Dehghani et al. (2021) seek to understand how a proactive transhipment policy can prevent shortages and minimise wastage. To this end, the authors develop a stochastic programming model that considers a network of demand nodes with uncertain demand. Each demand node decides on the quantity to order from a blood centre and on the quantity to be transhipped to other demand nodes in each review period. This decision support tool allows for calculating the optimal order and transhipment quantities that minimises total costs. The key conclusion is that cost benefits can be obtained when implementing a proactive transhipment policy, namely by reducing the safety stock levels and wastage. Dehghani & Abbasi (2018) note that transhipment is sometimes carried out based on the age profile of blood products in demand nodes. As such, the authors propose a new transhipment policy in which smaller demand nodes, that typically face smaller average daily demand, transhipment units aged over a given threshold to larger demand nodes. As these demand nodes observe greater demand, transhipped units can be transfused more easily, whereas if they remained at smaller demand nodes, there would be a greater risk of being discarded due to outdating. The work introduces a reactive transhipment policy, as larger demand nodes only require the transhipment of blood products when they run out of stock. The authors conclude that placing emergency orders whenever a demand node is in stockout is by no means a good practice in terms of cost and that the suggested transhipment policy allows for significant cost savings. In addition, an improvement in the average age of blood products transfused was observed, which is desirable and important for the performance of the BSC, since doctors usually prefer to use fresher blood (Pirabán et al., 2019).

2.2.3. Performance measures in blood supply chain management

Performance measures are indicators that support managers in decision-making, constituting a means of evaluating results, policies, processes, among others. In the context of BSC management, performance measures are particularly relevant as they allow an assessment of whether the defined objectives are being achieved. Since the ultimate goal of any BSC is to ensure the supply of blood products in sufficient quantity to meet demand, one of the most frequently adopted performance measures is the shortage rate. Duan & Liao (2014) define the shortage rate as the fraction of the demand that a blood centre or demand node cannot meet at any given time from the available inventory. In addition, outdated blood products are neither ethically nor economically desirable, so the outdated rate is often adopted as a performance measure. The outdated rate is the fraction of total units of blood products that are discarded after exceeding their shelf life (Duan & Liao, 2014). According to Beliën & Forcé (2012), shortages and outdates are indeed the most common categories of performance measures. The authors identify four other relevant categories, namely deliveries/ transportation costs, availability, safety, and processing times. The first category is characteristic of problems in the distribution process. Availability is associated with shortages, as it considers measures such as inventory levels, service level and days of supply, i.e., the quantity of units in inventory expressed in

days of consumption. The safety of blood products is often expressed in terms of the residual shelf life at transfusion and is a quality measure. Finally, the category processing times refers to collection and is particularly relevant to supply problems. Also in the context of collection, Alfonso et al. (2012) study the modelling and simulation of blood collection systems in France and evaluate the resulting model through a set of performance measures. These are classified into global and operational measures. The former include the service level, which the authors evaluate as the percentage of donors completing the donation within a target waiting time, the waiting fraction, i.e., the percentage of donors who have to wait at some phase of the collection process, the probability of abandonment, and the total cost. Operational measures include flow oriented measures such as the total amount of WB, RBCs and PLTs collected, and resource, both physical and human, utilisation measures.

In the BSC literature, the problems investigated consider single or multiple objectives and there is a wide range of other specific performance measures (Pirabán et al., 2019). Behzad Zahiri & Pishvaee (2017) present a network design model to solve a multi-period location-allocation problem, which aims to minimise total costs and maximise the balance and equity between the level of demand satisfaction of different zones. Chaiwuttisak et al. (2016) address a problem of low-cost collection and distribution centres location through a binary integer programming model that aims to improve blood product supply and reduce transportation costs. Hamdan & Diabat (2020) present a stochastic optimisation model aimed at minimising the cost of distributing blood products to demand nodes in a disaster case. Also considering disaster scenarios, Fahimnia et al. (2017) develop a bi-objective stochastic SC design model intended to minimise delivery time and supply costs. In vehicle routing problems, such as the one addressed by Gunpinar & Centeno (2016), a relevant performance measure is the minimisation of distances travelled, in this case by bloodmobiles. Doerner et al. (2008) also investigate a routing problem, which considers several time windows for the pickup of blood donations, and propose to minimise total driving time. Hemmelmayr et al. (2010) investigate vendor-managed inventory and develop technology to find delivery routes for blood products from blood centres to demand nodes, aiming to minimise the cost of planned and urgent deliveries. Among this research, many consider cost minimisation as an objective, thereby being a relevant and very frequent performance measure.

2.3. Supply chain network design

SCND is one of the most important activities in SCM as it determines the physical configuration of the SC network, i.e., the quantity, type, location and physical characteristics of the facilities (Govindan et al., 2017). In addition, it can involve the selection of technology and suppliers, the allocation of markets to the various facilities, the establishment of material and/or product flows between facilities, among others (Tordecilla et al., 2021). This is a problem that stems from a set of strategic planning decisions associated with large initial investment values, and it is generally not possible to change the network configuration in the short term (Govindan et al., 2017). In this sense, the network design of the SC is determinant both in the definition of the cost structure, and consequently in the profitability, as well as in the performance of the SCs, affecting the tactical and operational planning decisions (Farahani et al., 2014). In the literature, this is a subject on which there is plenty of research, not only because of its strategic relevance but also because of the vastness of SCs with very distinct characteristics that make

the problem even more complex. Some of these works are dedicated to redesigning the network of the SC, thus considering a pre-existing network that should be optimised (Eskandarpour et al., 2015; Govindan et al., 2017). According to Govindan et al. (2017), most work addresses single-period decisions, i.e., decisions considering only one time horizon, and relating to facilities of one or two echelons. Some deal with the flows of materials and/or products between facilities in the same echelon – intra-echelon flows; others consider flows between different echelons. If it is assumed that a facility can only be supplied by a single other facility at the upstream echelon, then the problem is said to be single-sourced as opposed to multi-sourcing problems. Furthermore, mathematical models of SCND problems cover several parameters, the most common being demand, cost, capacity, and supply. These models can have one or more objectives and cost minimisation is often the predominant factor in network design (Tordecilla et al., 2021). The ultimate goal of SCM is to meet customer demand and, in fact, the SCND problem often seeks to achieve it in the most cost-effective way. However, in recent years, new paradigms have emerged that have forced this problem to be rethought and transformed. The most frequent paradigms in literature are depicted in Figure 4.

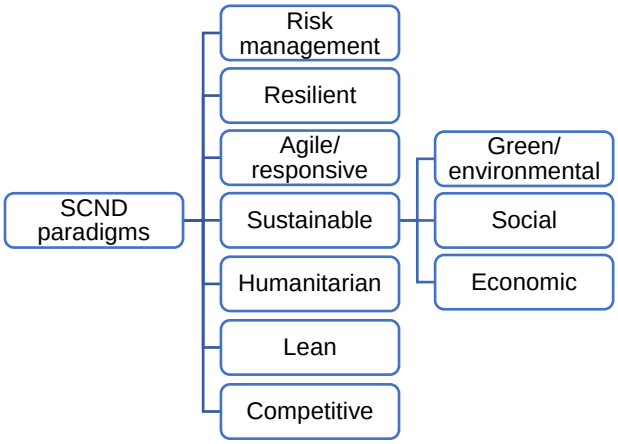

Figure 4 - Most frequent SCND paradigms in the literature

Any SC is subject to risks, i.e., undesirable situations that can compromise its performance, impacting both profitability and the service level provided. Govindan et al. (2017) and Tordecilla et al. (2021) categorise risks into operational and disruptive. Operational risks are the particular risks of each SC, which may be associated with the uncertainty of demand, supply, lead times and costs. Disruption risks are associated with events that are difficult to predict, such as natural disasters or pandemics, and can severely constrain the operation of SCs and enhance the impact of operational risks. A pandemic is a peculiar case of disruption, as it is a long-term phenomenon. The act of identifying, prioritising, monitoring and controlling risks is called risk management, which is a growing concern in network design problems (Farahani et al., 2014). Thus, the risk management paradigm aims to incorporate risk considerations into these problems and it is closely related to the design of robust and resilient networks.

In the literature, the resilience of a SC is defined as the ability, in the face of a disruptive event, to quickly return to the initial state without a significant compromise to SC performance, or even reach a new more advantageous state (Tordecilla et al., 2021). Thus, the resilient SCND paradigm focuses on managing the risks arising from disruptive events through the implementation of mitigation or contingency measures. Mitigation measures are adopted before disruptions occur. Examples of these

are visibility, which consists of the detailed monitoring of the route of materials and products throughout all stages of the SC by the entities involved in it, and collaboration between these entities, entailing information sharing. Contingency measures are taken only after the disruption occurs and integrate, among others, multiple sourcing and spot purchasing, i.e., purchases to meet immediate needs without necessarily following the sourcing strategy in place (Govindan et al., 2017; Tordecilla et al., 2021). Tordecilla et al. (2021) work on this topic through a review of resilient SCND papers using simulation-optimisation methods. The authors consider that resilience cannot be properly addressed without considering long-term decisions such as the network design. They conclude that since designing extremely resilient networks would involve large financial efforts, it is important to consider the trade-off between resilience and financial performance. To assess the resilience of SCs, Fattahi et al. (2020) propose recovery time and loss of performance due to disruptive events as key performance measures.

Sometimes, in the light of changes in consumer demand patterns, for example, there is a need to redesign the SC network. The paradigm of agile SCND stems from these situations, as it is important to act quickly to deliver products or services that meet these emerging needs. This paradigm can also be called responsive, and requires the various entities in the SC to be flexible, a characteristic that can result from the adoption of highly innovative technologies (Farahani et al., 2014; Tordecilla et al., 2021).

Sustainability is a concept that generally refers to the consumption of resources at a lower rate than their regeneration, so as not to compromise the satisfaction of future needs. Based on this concept, the paradigm of the sustainable SCND emerged, which aims to define the configuration of networks integrating considerations related to the three dimensions of sustainability – green/environmental, social, and economic. Eskandarpour et al. (2015) focus on reviewing sustainable SCND work, targeting optimisation issues. The authors conclude that work addressing all three dimensions is scarce and that the environmental dimension has been much more explored than the social one. They believe that this is due to the difficulty in mathematically modelling social factors such as working conditions, social equity, compliance with human rights, among others. However, they warn that the evaluation of the environmental dimension has been limited to greenhouse gas emissions. Moreno-Camacho et al. (2019) also present a review of SCND work that addresses at least two dimensions of sustainability and in which they aim to identify the indicators used to assess sustainability. The conclusions drawn by the authors are in line with the previous ones, i.e., the social dimension continues to be poorly addressed.

Logically, not all SCs are profit-driven, as some are non-business, such as the humanitarian ones. The humanitarian SCND paradigm emerges to deal with humanitarian emergencies following natural or man-made disasters that affect the normal functioning of SC facilities, the land links for supplying materials or flowing products, or even information flows. It aims to establish networks that can promptly provide relief to populations, and these can be dedicated to the provision of food, healthcare or other services (Govindan et al., 2017).

The lean SCND paradigm is derived from the lean manufacturing philosophy. This aims to increase the overall efficiency of SCs by eliminating activities that do not add value or rethinking others, and strives to reduce total costs (Farahani et al., 2014). However, Tordecilla et al. (2021) consider that this paradigm undermines the resilience of SCs, in the sense that by eliminating redundancies it increases vulnerability to risk events.

Finally, Farahani et al. (2014) review SCND work with particular emphasis on competitive environments. The competitive SCND paradigm is distinguished by safeguarding the impact of competition on network design, with the aim of improving the future competitiveness and performance of the SC. The authors state that most network design work in the literature ignores the impact of new competitors and existing competition on consumer behaviour. Accordingly, they develop a framework to help decision-makers model competitive SCND problems. This requires decision-makers to identify the type of competition involved and the competitive factors, e.g. quality and price, as each situation requires a distinct modelling structure. Govindan et al. (2017) classify competitive environments into (1) competition between similar facilities in the same SC, (2) competition between distinct facilities in the same SC, and (3) competition between distinct SCs.

This being said, it follows that the decision-making environment for SCND is rather complex and uncertain. On the one hand, there are highly unpredictable risks to be taken into account and, on the other hand, given that it concerns long-term decisions, it is important to note that the most common parameters are not deterministic, changing over time (Moreno-Camacho et al., 2019). Thus, uncertainty emerges as a key planning factor and several recently published research papers consider it.

2.4. Uncertainty in the context of the supply chain network design

In the literature, it is consensual that SCND problems with uncertainty are complex and it is not always possible to solve them in acceptable timescales. SCND problems under uncertainty aim to configure networks that ensure the regular performance of SCs whatever the environment in which they are inserted, and there are different quantitative approaches to address them (Govindan et al., 2017). According to Tordecilla et al. (2021), these are mainly divided into optimisation and simulation, although in recent years several hybrid approaches have been developed. The authors observe that the use of optimisation is more popular than simulation since the latter does not allow obtaining optimal or near-optimal solutions. Nevertheless, they point out that in the field of simulation, discrete-event simulation and Monte Carlo simulation are the most commonly used techniques. With regard to mathematical approaches to modelling optimisation problems, the most popular are stochastic programming, robust optimisation, and fuzzy programming. The relevant quantitative approaches in the literature of SCND under uncertainty are presented in Figure 5. In particular, the optimisation techniques are detailed below.

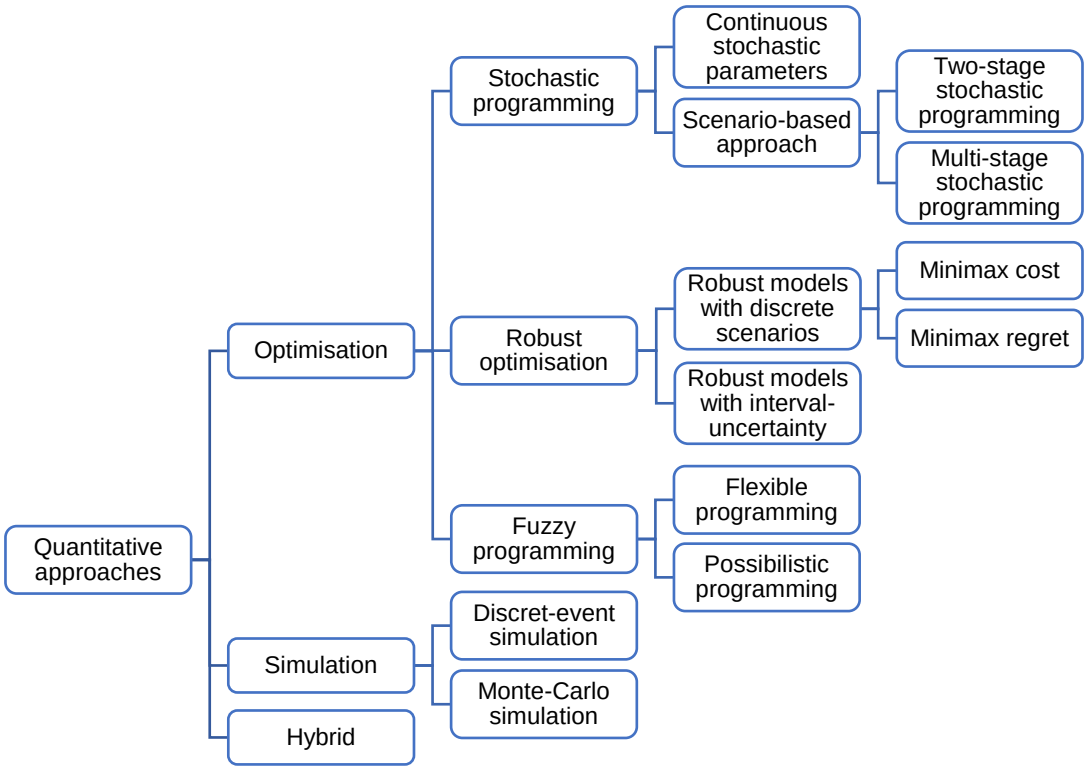

Figure 5 - Quantitative approaches to uncertainty in the context of SCND

Govindan et al. (2017) review a large body of work on SCND under uncertainty and describe the main mathematical approaches to the subject. Stochastic programming is suited for decision-making environments in which the probability distributions of uncertain parameters are known. These parameters, called stochastic, can be continuous or discrete, which triggers different approaches. The use of continuous stochastic parameter models to solve SCND problems is not common, because continuous distributions are difficult to model. In the case of relatively simple problems, which regard only the location of similar facilities, this may be an approach to consider. However, in the case of problems that deal with the location of different facilities of the SC, resorting to this approach often results in models that are computationally intractable and therefore prove to be of little use in solving the problem. Thus, the most common approach is scenario-based which allows to consider dependencies between parameters. Scenarios can be predetermined and characterised by known probabilities, or generated, so that they are as appropriate as possible to the problem. Scenario-based stochastic programming essentially applies to two types of problems, so it is subdivided into two approaches – two-stage stochastic programming and multi-stage stochastic programming. According to the authors, two-stage stochastic programming is the most widespread approach. The first stage corresponds to decision-making at the strategic planning level, such as the location of facilities and their capacity, and takes place before the realisation of the uncertain parameters; the second stage corresponds to decision-making at the tactical and operational planning level, such as the definition of transport flows between facilities. Multi-stage stochastic programming applies to situations in which decisions must be non-anticipative, i.e., they must not depend on the future values of uncertain parameters. In these cases, decisions are made sequentially and decision-makers can intervene between decisions.

Robust optimisation is used in decision-making environments where there is little or no access to historical data and it is not possible to estimate the probability distributions of uncertain parameters. These are therefore unknown (Heidari-Fathian & Pasandideh, 2018). Also, robust optimisation allows decision-makers to decide about the level of robustness of the model to apply to the SCND problem (Hamdan & Diabat, 2020). This means that decision-makers can approach problems taking into account their degree of risk aversion (Habibi-Kouchaksaraei et al., 2018). As such, robust optimisation is particularly relevant in developing worst-case optimisation models of SC network performance and can be used in both single-objective and multi-objective optimisation models (Govindan et al., 2017; Hamdan & Diabat, 2020). Uncertain parameters can be continuous or discrete, and there is a specific approach for each of these. In the case of continuous parameters, the most appropriate approach consists in considering that these parameters can be varied within certain uncertainty values – robust models with interval-uncertainty. This is an approach that usually guarantees feasible solutions and computationally tractable models. In the case of discrete parameters, the most appropriate approach considers several scenarios – robust models with discrete scenarios (Govindan et al., 2017). In this regard, two types of robustness exist in the literature – solution robustness and model robustness. A solution is considered robust when it is nearly optimal for all scenarios and a model is robust when the solution obtained is nearly feasible for all scenarios (Habibi-Kouchaksaraei et al., 2018). Finally, also robust models with discrete scenarios comprise two alternatives. The minimax cost intends to minimise the maximum cost of all scenarios, and the minimax regret intends to minimise the regret, i.e., the difference between the cost of a solution and the cost of the optimal solution for a given scenario (Govindan et al., 2017).

Fuzzy programming applies to decision-making environments whose uncertainty is non-probabilistic. There are two approaches – flexible programming and possibilistic programming (Eskandari-Khanghahi et al., 2018). Flexible programming assumes that the values of uncertain parameters are set by the decision-makers, so they are subjective (Jafarian et al., 2018). Consequently, this approach considers flexible objective function target values, which are derived from decision-makers' expectations, and elastic constraints, i.e., constraints whose violation is acceptable to some extent, but which implies a penalty on the objective function (Eskandari-Khanghahi et al., 2018). In the possibilistic programming approach, the uncertain parameters values and the formulation of the model constraints are based on available quantitative data and the qualitative insights of the decision-makers (Eskandari-Khanghahi et al., 2018). In both approaches the involvement of decision-makers, who intervene in the degree of satisfaction of the objective functions, is notorious (Samani et al., 2019).

Once the mathematical approaches to model the SCND problem have been presented, it is important to introduce the solving approaches to be applied to these models. Among these are the exact methods and metaheuristics (Tordecilla et al., 2021). The main difference between these is that exact methods guarantee that optimal solutions are obtained for the optimisation problems, which is not the case for metaheuristics. SCND problems under uncertainty are usually tackled using solvers, such as GAMS or LINGO, and the execution can be extremely time-consuming when using exact methods, particularly if the models are complex and with large instances. Execution time is a very relevant factor that often impels the usage of metaheuristics, in detriment of optimality, since these allow solving problems in acceptable time intervals. Specifically, the exact methods are associated with integer

programming and include the branch-and-bound algorithm, dynamic programming, Lagrangian relaxation based methods, among others (Puchinger & Raidl, 2016). Out of these, the Lagrangian relaxation stands out, since it allows to simplify highly complex models and, therefore, to reduce the time required to solve them. It consists in the relaxation of constraints that are then associated with the objective function as penalty functions (Heidari-Fathian & Pasandideh, 2018). Briefly, upper and lower bounds are obtained, between which lies the value of the optimal solution, which allow decision-makers to assess how close they are to that solution. This procedure is iterative and enables the gap between the two limits to be reduced (Fahimnia et al., 2017). Metaheuristics include, for example, simulated annealing, tabu search, self-adaptive differential evolution and variable neighbourhood search algorithms. Both exact methods and metaheuristics can be combined, which can be observed in the SCND literature (Puchinger & Raidl, 2016).

2.5. Previous work on blood supply chain network design

The BSC has been frequently addressed in the literature over the last decades, with emphasis on inventory management. Recently, the subject of SCND under uncertainty has assumed particular relevance. Jabbarzadeh et al. (2014) address disaster situations and formulate a blood SCND model using scenario-based stochastic programming. This optimisation model aims to determine the number and location of multi-echelon blood facilities, the collection quantity in each of them and their inventory levels. To this end, the authors consider both demand and supply as uncertain parameters, and multiple scenarios, during and post-disaster. The resulting model has the single objective of minimising the total cost of the network to be configured and is applied to a case study in Iran. Ramezanian & Behboodi (2017) also devote their research work to a real case in Iran. The authors, aware of the importance of collecting an adequate supply of blood to meet demand, develop a model to locate BSC facilities and to allocate donors to these facilities. This model considers social aspects, such as the distance of donors to collection facilities, the collection experience of donors, and the budget spent on advertising collection actions, to derive a utility function. In practice, the authors' goal is to reduce shortages by increasing utility. They consider two approaches – a deterministic one and another that incorporates demand uncertainty. With regard to uncertainty, the paper models the problem through a robust optimisation mathematical approach that is solved using a mixed-integer linear programming model, an exact solution method. As in the previous work, also Ramezanian & Behboodi (2017) consider a multi-period planning horizon and a single objective function that minimises several costs.

As already mentioned, in addition to shortages, wastage is also undesirable. Fahimnia et al. (2017) find that in case of disaster, the Iranian BSC is not faced with donation deficit, but rather with a very inefficient distribution, resulting in wastage. In this context, the authors propose a bi-objective scenario-based stochastic optimisation model that considers multiple echelons and demand and supply uncertainty. It attempts to minimise both costs and distribution time and, given the complexity of the model, the ε-constraint method and a Lagrangian relaxation based method are adopted. The ε-constraint method is often applied in multi-objective optimisation programming and aims to obtain single objective models. To this end, all but one of the objectives of the initial model are converted into constraints for which an upper bound is defined. The model is solved iteratively and a virtual grid is

defined in the solution space which, if sufficiently fine, allows obtaining all optimal solutions from the Pareto frontier.

Zahiri & Pishvaee (2017) develop the first work to incorporate blood type compatibility into a SCND model. In addition, the authors combine two distinct mathematical approaches to model the problem. The uncertainty of parameters such as demand and supply is considered through possibility distributions, so the model initially developed is a possibilistic programming model. However, the authors consider that this fuzzy approach has limitations, such as the difficulty in controlling the deviations of the objective function from the planned performance. Thus, they propose a hybrid approach that results in a robust possibilistic programming model. In what concerns the solution approach, they formulate a multi-period mixed-integer linear programming model. This is bi-objective and aims at minimising total network costs and unmet demand. The authors conclude that their work, applied to a case study of an Iranian province, allows quite significant cost savings when compared to others in the literature to date.

Heidari-Fathian & Pasandideh (2018) focus on the network design paradigm of sustainable, in particular green, SCs. The authors account for both demand and supply uncertainty and multi-echelons. They approach the problem through robust optimisation and develop a theoretical multi-objective mixed-integer linear programming model. Specifically, the model has three objective functions that aim to minimise the total network costs of the BSC, shortages and the amount of perished blood products, and greenhouse gas emissions resulting from transportation activities. In order to simplify the model, the authors employ a method similar to the ε-constraint method, which they call Bounded Objective Function. This method allows them to deal with only one objective function. In addition, they apply a Lagrangian relaxation based method that they encode using the GAMS solver. Also Habibi-Kouchaksaraei et al. (2018) resort to robust optimisation. In this case, the authors propose to determine the quantity and location of three-echelon blood facilities under different disaster scenarios. Therefore, they develop a multi-period robust model with discrete scenarios. It is a bi-objective model that minimises network costs and blood product shortages, and the authors conclude that in the Iranian context it is possible to configure a disaster robust BSC network with an acceptable budget.

Although stochastic programming and robust optimisation are the most common mathematical approaches to model BSC network design problems under uncertainty, some authors explore fuzzy programming. This is the case of Eskandari-Khanghahi et al. (2018), who adopt a possibilistic programming approach. The authors focus on situations during and post-disaster and develop a multi-period mixed-integer linear programming optimisation model to determine not only the location and capacity of facilities, but also the size of each shipment and the most efficient vehicle routes. This formulation considers three objective functions, which aim to reduce the environmental impact associated with the network configuration, maximise the social effects, namely job creation, and minimise total costs. Regarding the solution approach, the authors use metaheuristics, namely the simulated annealing algorithm.

Samani et al. (2019) develop a robust optimisation approach that incorporates several relevant quantitative and qualitative attributes in the design of the BSC network. The authors aim to maximise the number of blood collection facilities and collection capacity, minimise the loss of blood product freshness, and minimise total costs. Thus, they formulate an integer programming model, an exact

solving approach, considering multiple periods and three objective functions. Network costs and blood product freshness are examples of quantitative attributes. Qualitative attributes are considered to be availability, market environment, and transport and traffic conditions. Regarding uncertainty, in addition to demand and supply, the various cost factors are treated as uncertain parameters. The authors conclude that it is critical for decision-makers to account for quality-based requirements when designing a network, as qualitative attributes can significantly influence the locations of facilities. Hence, they recommend that these strategic planning decisions should not be based greatly on economic concerns.

The work of Hamdan & Diabat (2020) falls within the paradigm of resilient SCND and presents a two-stage stochastic programming model, the first stage corresponding to pre-disaster planning and the second one to post-disaster planning. It is a multi-echelon bi-objective model that is applied to a real case study in Jordan and minimises both the cost and time of delivering blood products to demand nodes in a disaster context. As such, it contemplates the possibility of disruption of BSC facilities and routes. Given the complexity of the model, the authors apply a method based on Lagrangian relaxation. Finally, they highlight that the donation rate is a major factor in the timely distribution of blood products. Also Haghjoo et al. (2020) investigate a blood SCND design problem under risk of disruption. However, the authors choose to model the problem using the robust optimisation approach with discrete scenarios. Among the assumptions, it is highlighted that the effect of disruptive phenomena on blood facilities depends on the initial investment associated with the establishment of these facilities. The resulting multi-period location-allocation model considers demand as an uncertain parameter excluding supply, minimises total costs, so it is single-objective, and is applied to a real case of an Iranian province. Regarding the solution approach, metaheuristics are chosen, in particular the self-adaptive imperialist competitive algorithm and invasive weed optimisation.

Recently, Arani et al. (2021) model a specific blood SCND problem – sustainable lateral resupply. This is a problem that aims to implement a network in which storage and inventory are designed in order to facilitate the distribution of blood products to demand nodes and between demand nodes. In addition to this, it considers the routing of vehicles, so it is an integrated problem. The authors approach it through scenario-based stochastic programming and solve it using mixed integer programming. The model developed is multi-objective. Specifically, it minimises total costs and the environmental impact associated with the implementation of the network, and maximises job openings, thus considering the three dimensions of sustainability. Furthermore, four echelons, demand and supply uncertainties, shelf life of various blood products and ABO/Rh compatibility are considered.

2.6. Chapter conclusions

This chapter presented a review of the BSC literature, with emphasis on the topic of network design under uncertainty. First, the concepts of SC and SCM were introduced. The network configuration of centralised SCs, the facilities that comprise them and the processes they perform were also presented. As four echelons were considered, these were detailed in order to clarify how the BSC works. A set of common performance measures in the management of BSCs was also presented. Although the literature highlights that inventory management has been the most addressed topic, recently others have been targeted for investigation. This is the case of network design. A SCND review was carried out in

which seven emerging paradigms were identified and it was concluded that it is fundamental to consider uncertainty in these problems. Thus, a set of mathematical approaches to uncertainty were made explicit. Finally, a review of the literature on blood SCND under uncertainty was conducted. The existing works are recent but scarce. Appendix A presents Table A1 that summarises the contribution of these works to the literature. This shows that despite the evident uncertainty associated with supply, not all works consider it. With regard to mathematical approaches, there is no clear trend, although stochastic programming and robust optimisation are the most widely used. Contrarily, there is a predominant solution approach – exact methods. In general, existing works focus on cost minimisation, this being a common goal to all, although some integrate environmental and social considerations. The models formulated are often applied to real case studies and the overwhelming majority focus on Iranian provinces.

To conclude, from the literature review presented it is inferred that the topic of blood SCND under uncertainty still lacks research. Thus, the future development of this study involves formulating an optimisation model to address this problem, i.e., one that helps in deciding which are the best locations for blood facilities, considering that both demand and supply are uncertain. Accordingly, Chapter 3 is presented next, which describes in detail the problem at hands, and the developed model to handle the blood SCND under uncertainty.

3. Problem statement and model formulation

This chapter aims to first present the main characteristics of the BSC design problem under uncertainty, given the literature reviewed. Next, the mathematical formulation of the comprehensive generic model developed to address such a problem is described. To this end, it is divided into three sections. Section 3.1. consists of the problem statement, which includes a detailed description of the problem, the decisions that the model supports, its assumptions and the performance measures adopted in the evaluation of the model results. Next, Section 3.2. presents the mathematical formulation of the optimisation model and is divided into four subsections. First, Subsection 3.2.1. describes the approach followed in dealing with the uncertainty inherent to the problem. Subsection 3.2.2. presents the notation used in the model and is further divided into three other subsections – sets, parameters and variables. Subsection 3.2.3. presents the various plots that constitute the objective function and Subsection 3.2.4. presents the model constraints duly justified. Finally, Section 3.3. concludes the chapter.

3.1. Problem Statement

The optimisation model developed to deal with the blood SCND under uncertainty contributes to filling gaps in the literature to date. Key tactical-strategic planning decisions, such as the establishment of blood facilities and the selection of their capacity level, as well as allocation decisions, are covered. However, the BSC is characterised by a number of particularities that make it complex to manage. This is the case with the variety of blood products and types. Also, the different processes of each echelon are relevant. For example, there are few works that address the collection method, despite the fact that it directly influences the yield of the fractionation process. However, the model is not restricted to the collection echelon, as it also addresses processes of the remaining three echelons – production, inventory and distribution, in order to treat the network as a whole. Therefore, the conceptual model of the problem is presented in Figure 6 and the processes of each echelon are highlighted in different colours.

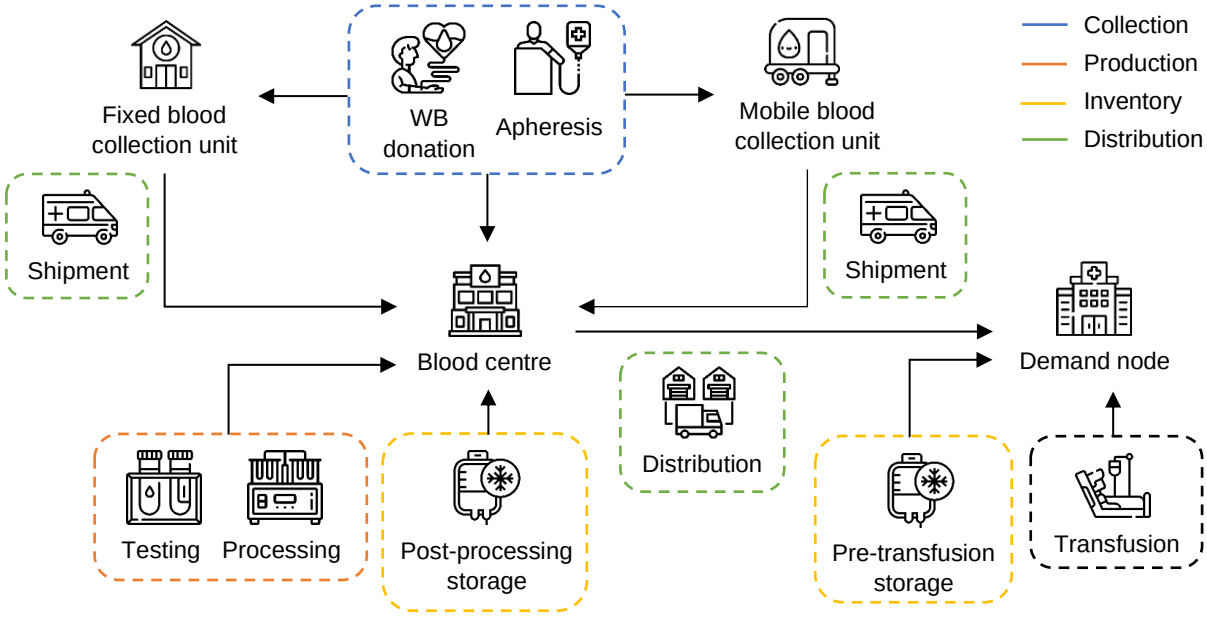

Figure 6 - Conceptual model highlighting blood facilities and processes

Problem description

The collection starts when the donor groups ($i \in I$) travel to the various collection sites. Since SCND comprises the physical configuration of the SC and therefore tactical-strategic planning decisions, collection at mobile collection sites, such as bloodmobiles and mobile venues, is often outside the scope of the problem. This is because the planning of these collection sessions involves tactical-operational decisions, such as the selection of the various temporary locations, the scheduling and promotion of the collection sessions, the allocation of human resources, among others. In what concerns bloodmobiles, there is also the need to plan the routes of the vehicles' daily travels. However, related literature recognises that donations in mobile venues are significant. In fact, this is the prevalent collection model in many countries, as it allows reaching locations distant from fixed collection sites that otherwise would not donate blood (Williamson & Devine, 2013). Thus, it is important to consider the supply from mobile venues. Having said that, the model considers three sources of donations – from fixed blood collection units ($j \in J$), such as hospital blood units, from blood centres ($k \in K$) and from mobile blood collection units ($n \in N$), which aim to represent mobile venues. However, for decisions on the location and capacity selection of facilities, only fixed blood collection units and blood centres are considered. Donations from mobile blood collection units thus constitute a source of external supply. A set of pre-established mobile blood collection units, whose locations do not change over the planning horizon, is considered. These locations are external donation supply points.

Upon arrival at the collection facilities, donors may either donate WB or opt for component apheresis. The method of blood donation ($m \in M$) is relevant as it affects the yield of donations and, consequently, the number of blood products ($p \in P$) that are derived from them. In the case of donations from mobile blood collection units, these are restricted to WB, as such units are generally not equipped with the resources required for apheresis collection. Also, the model accounts for the various blood types ($b, b' \in B$) and the substitutability relationships between them.

After collection, donations originating from fixed and mobile blood collection units are sent to blood centres. With regard to the shipment process, the model should assist in the decision making regarding the allocation of collection units to blood centres. In blood centres, donations are then tested and processed according to the collection method from which they originate. Subsequently, the resulting blood products are stored in inventory until they are requested by demand nodes ($h \in H$). Although the inventory echelon includes storage and inventory management processes, only post-processing and pre-transfusion storage are taken into account in the model. Inventory management assumes that the perishability of blood products is taken care of. However, given that the shelf life of these products is only a few days, with the exception of plasma and cryo, and given that planning periods ($t \in T$) in tactical-strategic models are several months, it does not make sense to consider the shelf life and hence the inventory management process. As such, it is considered that there is no inventory carryover between periods. It is only considered that all blood products produced in a given time period are stored and those not shipped in that same period constitute wastage.

After storage, blood products are distributed to demand nodes according to the orders placed by them. The model should also be a support tool regarding the allocation of demand nodes to blood centres. That is, each demand node has an assigned blood centre to which it must place its orders. In

the event that the quantity requested by the demand nodes to a blood centre is greater than the quantity produced in that period, there is a shortage of the blood product concerned. Conversely, if the quantities requested by a demand node are higher than the demand observed in the period concerned, then there is wastage at the demand node. Furthermore, it should be noted that the model does not contemplate lateral transshipment between blood centres nor between demand nodes, given the operational nature of the process.

Finally, it is important to mention that the model addresses the uncertainty inherent to the supply and demand parameters by resorting to two-stage stochastic programming, whereby various scenarios ($s, s' \in S$) are considered. Further details on this approach are provided in Subsection 3.2.1.

Model decisions

To summarise, the strategic decisions for which the model is a support tool are:

- in which locations should fixed blood collection units be established and what is their collection capacity;
- in which locations should blood centres be established and what are their collection, processing and storage capacities;
- which fixed blood collection units should be allocated to which donor groups;
- which mobile blood collection units should be allocated to which donor groups;
- which blood centres should be allocated to which donor groups;
- which blood centres should be allocated to the established fixed blood collection units;
- which blood centres should be allocated to which mobile blood collection units;
- which blood centres should be allocated to which demand nodes.

All allocation decisions are constrained to maximum distances. That is, there are limits to the distance donor groups must travel in order to donate at any of the collection facilities. This is a relevant consideration as it reflects a social aspect. Given the downward trend in the number of donors, it is paramount to encourage donation by bringing collection facilities closer to the population and minimising the inconvenience that travelling may cause them. In addition, there are limits to the maximum distance between both fixed and mobile blood collection units and blood centres, and also between blood centres and demand nodes, in order to streamline the processes that take place across these facilities. Further details are provided below in the presentation of the constraints on distances, in Subsection 3.2.3.

Additionally, the results of the model provide information on several quantities resulting from tactical decisions. Among these, the following stand out:

- the quantities of each type of blood collected in each collection facility and by what method;
- the quantities of each blood product and type produced;
- the quantities of each blood product and type distributed to the demand nodes;
- the quantities of each blood product and type substituted by other compatible blood types;
- the quantities of each blood product and type wasted, if any, in blood centres and demand nodes;
- the quantities of each blood product and type in short supply, if any, in blood centres and demand nodes.

The latter is particularly important as the model does not impose that demand be fully met. Thus, shortages will make it possible to determine the service level of the BSC. All other quantities that the model provides are duly characterised below, in Subsection 3.2.2.3.

Assumptions

Understandably, the model has some assumptions, as it is not possible to model in detail the entire operation of the aforementioned SC. Among the assumptions, the topic of inventory management and blood product shelf-life stands out because (1) it is assumed that there is no inventory transition between periods over the planning horizon, which may actually occur. As noted above, accounting for the shelf life of blood products is operational in nature. This assumption may have implications on wasted quantities, which, consequently, may be higher than in the real SC operation. The same holds for the assumption of not considering the lateral transshipment process, because (2) the model does not cover inventory redistribution between blood centres or demand nodes. Thus, the quantities of blood products that the model reveals as wastage may also be magnified. On the supply side, the external supply of blood donations is also an assumption as it is assumed that (3) there are mobile blood collection units whose location is unchanging over time. The purpose of these is only to simulate the supply coming from the mobile venues that are generally scattered daily throughout the territory. Finally, it is known that donors have to take a time gap between consecutive donations and the length of this gap depends on the method of blood donation. As this is a tactical-strategic optimisation model, donors are obviously not treated individually but as groups of donors and (4) the deferral time is not safeguarded.

Performance measures

The results of the model will be evaluated through a set of performance measures, according to the established objectives. The aim is to optimise the functioning of the Portuguese BSC as a whole, considering three fundamental pillars – cost, wastage and carbon emissions. Social aspects are addressed through a set of constraints. Thus, the performance of the optimised SC will be assessed by:

- Monetary cost – analysis of the cost components associated with each of the echelons;
- Established blood facilities – analysis of their distribution and geographical coverage;
- Blood product wastage – analysis and comparison between quantities collected, produced and effectively distributed;
- Shortage of blood products – analysis of the service level through the percentage of demand satisfied;
- Substitutability between blood types – analysis of the quantities distributed in substitution of the blood types demanded, also being an indicator of the service level provided;
- Carbon emissions from transportation.

3.2. Mathematical formulation of the model

This section presents the mathematical formulation of the optimisation model that aims to be very comprehensive. This is based on several works, in particular that of Samani et al. (2019), which presents a mixed-integer linear programming model. The major differences between the model of Samani et al. (2019) and the one developed are that the former considers a set of disposal centres for the treatment

of wasted blood products. However, existing information in the literature about the process of treatment of unused blood is scarce and no details are known. Hence, the disposal centres are not included in the model developed. The work of Samani et al. (2019) does not address the different blood types and, consequently, the substitutability relationships between them, which is an asset in the following generic model. Also, the list of variables in Samani et al. (2019) does not include shortage variables as the model guarantees demand satisfaction. This is not the case in the developed model, which adopts a more realistic approach. It is not possible to guarantee that demand will be fully met if there is not a sufficient supply of either the required blood type or compatible blood types. In such situations, it may be necessary to import blood products and there is European legislation in place for this purpose (European Commission, 2016). Contrarily, Samani et al. (2019) consider inventory variables and thus the shelf-life of blood products. The authors characterise their work taking into account a tactical-strategic planning horizon, yet the inventory matters are operational. With regard to decisions to be made, the authors identify which locations to set up blood facilities, the allocations of donor groups to collection facilities and also of collection facilities to blood centres. It, therefore, does not address capacity selection decisions, which are fundamental to network design. Decisions affecting the capacity of blood facilities are supported in the work of Cortinhal et al. (2019). This work considers that whenever a facility is established in a candidate location, then a respective capacity level has to be selected. Thus, sets of capacity levels are defined for each type of facility to be established. Regarding the objective functions, the work of Samani et al. (2019) contemplates three – the first is economic, the second defines a function of blood product quality loss, dependent on the shelf-life of blood products, and the third is relative to a process of weighting qualitative factors. It is important to note that of these, only the economic objective function will be useful to the following model. The environmental component of the objective function of the model below is supported in the work of Heidari-Fathian & Pasandideh (2018), in the sense that carbon emissions will be directly proportional to variables representing quantities. Finally, Samani et al. (2019) opt for robust programming as an approach to uncertainty, however this is not the choice of the present work. The generic model developed employs a two-stage stochastic programming approach, which assumes that there are known historical data regarding the uncertain supply and demand parameters. In fact, in most developed countries, the information on donations collected and transfusions performed is known and publicly available, which allows extrapolating data and estimating supply and demand.

Next, Subsection 3.2.1 describes the outline of the two-stage stochastic programming approach employed in the model. Thereafter, Subsection 3.2.2. introduces the notation to be used in the mathematical formulation of the mixed integer linear programming model. Subsections 3.2.3. and 3.2.4. explain the objective function and constraints to be modelled, respectively.

3.2.1. Characterisation of the approach to uncertainty

To address uncertainty the model resorts to two-stage stochastic programming. Briefly, the decisions to be made are decided at two distinct moments – before and after the realisation of uncertainty. Key tactical-strategic decisions, such as the establishment and capacity selection of blood facilities, and allocations, are made before the values of the uncertain parameters are known. These

decisions are represented by binary variables and correspond to the first stage. In the second stage uncertainty-dependent decisions are taken. These relate to the quantities to be collected in each period, to be produced, to be distributed, among others, and are represented by positive variables.

Uncertainty in stochastic programming is handled through a set of scenarios, which Albareda-Sambola et al. (2013) define as "a realisation of all the uncertain parameters along all the periods of the time horizon". The scenarios have a known probability of occurrence and the variables associated with the decisions of the second stage depend on these.

Thus, at the beginning of the planning horizon a decision is made whether or not to establish a particular blood facility and, once installed, it remains open in all periods. That is, establishment decisions are not allowed to be changed between periods. Given the inherent costs of opening blood facilities, it would not make sense for them to be able to open and close throughout the planning horizon. Note that capacity selection decisions are simultaneous with establishment decisions, so capacity cannot be changed during the planning horizon either. With regard to decisions on the allocation of donors to collection facilities, of collection facilities to blood centres and of demand nodes to blood centres, these are also taken at the beginning of the planning horizon. As such, once an entity is allocated, it must remain allocated in all subsequent periods.

3.2.2. Notation

The model notation includes the sets, parameters and variables, and these are presented below.

3.2.2.1. Sets

The sets and indices used in the formulation of the model are as follows:

I	Set of donor groups indexed by i $(i \in I)$
J	Set of candidate and existing locations for fixed blood collection units indexed by j $(j \in J)$
Q_J	Set of capacity levels available in each potential fixed blood collection unit location indexed by q_j $(q_j \in Q_J)$
K	Set of candidate and existing locations for blood centres indexed by k $(k \in K)$
Q_K	Set of capacity levels available in each potential blood centre location indexed by q_k $(q_k \in Q_K)$
N	Set of mobile blood collection unit locations indexed by n $(n \in N)$
H	Set of demand nodes indexed by h $(h \in H)$
M	Set of blood donation methods indexed by m $(m \in M)$
P	Set of blood products indexed by p $(p \in P)$
B	Set of blood types indexed by b, b' $(b, b' \in B)$
T	Set of time planning periods indexed by t $(t \in T)$
S	Set of scenarios indexed by s, s' $(s, s' \in S)$

3.2.2.2. Parameters

The parameters required as input data to the model implementation are as follows:

Cost parameters

f_{jq_j}	The fixed cost of establishing a fixed blood collection unit located in j with the capacity level q_j
f'_{kq_k}	The fixed cost of establishing a blood centre located in k with the capacity level q_k
e_{jq_j}	The cost of equipping the fixed blood collection unit j with the capacity level q_j
e'_{kq_k}	The cost of equipping blood centre k with capacity level q_k
oc_m	The unit operating cost of blood donation by method m
pc_{pm}	The unit production cost of blood product p collected by the m donation method
ic_{pk}	The unit holding cost of blood product p at blood centre k
ic'_{ph}	The unit holding cost of blood product p at demand node h
$sc_{bb'}$	The unit cost of substituting blood type b with blood type b'
wst_p	The unit wastage cost of blood product p
stg_p	The unit shortage cost of blood product p
tc_{jk}	The unit transport cost of blood packages from the fixed blood collection unit j to blood centre k
tc'_{nk}	The unit transport cost of blood packages from mobile blood collection unit n to blood centre k
tc''_{kh}	The unit transport cost of blood products from blood centre k to demand node h

Capacity parameters

$ccap_{jq_j}$	The collection capacity of the fixed blood collection unit j with capacity level q_j
$ccap'_n$	The collection capacity of the mobile blood collection unit n
$ccap''_{kq_k}$	The collection capacity of blood centre k with capacity level q_k
$pcap_{pkq_k}$	The production capacity of blood product p in blood centre k with capacity level q_k
$scap_{pkq_k}$	The storage capacity for blood product p in blood centre k with capacity level q_k
$scap'_{ph}$	The storage capacity for blood product p at demand node h

Distance parameters

∂_{ij}	The distance between donor group i and fixed blood collection unit j
∂'_{in}	The distance between donor group i and mobile blood collection unit n
∂''_{ik}	The distance between donor group i and blood centre k
∂'''_{jk}	The distance between the fixed blood collection unit j and blood centre k
∂''''_{nk}	The distance between mobile blood collection unit n and blood centre k
∂'''''_{hk}	The distance between demand node h and blood centre k
mdc	The maximum distance between each group of donors and the nearest blood collection unit

mdp The maximum distance between each fixed or mobile blood collection unit and the nearest blood centre

mdd The maximum distance between each demand node and the nearest blood centre

Production parameters

φ_m The percentage of blood collected by method m that is used

δ_{pm} The production rate of blood product p donated by method m

Substitutability parameters

$\Delta_{bb'}$ ABO/Rh blood compatibility matrix (1 if the demand for type b blood product may be fulfilled by type b' and 0 otherwise)

$\nabla_{bb'}$ ABO group substitution priority matrix

Environmental parameters

ce_{jk} Carbon emission rate to transport each unit of blood donated in the fixed blood collection unit j to blood centre k

ce'_{nk} Carbon emission rate to transport each unit of blood donated in the mobile blood collection unit n to blood centre k

ce''_{kh} Carbon emission rate to transport each unit of blood product from blood centre k to demand node h

co_2c Carbon price

Uncertain parameters

s_{bits} The maximum amount of type b blood that is supplied by donor group i during period t in scenario s

dem_{pbhts} The demand for blood product p of type b at demand node h during period t in scenario s

Other parameters

π_s The probability of occurrence of the scenario s

ω A very large number

3.2.2.3. Variables

The two-stage stochastic optimisation model consists of two main types of variables – binary variables and positive integer variables. Binary variables concern strategic decisions that do not change over the planning horizon or according to the scenario considered, and therefore do not depend on the realisation of uncertainty. These decisions are the location and capacity selection of blood facilities, and allocations. Positive integer variables, in turn, are variables that depend on the realisation of the uncertainty associated with the problem. Therefore, their values rely on the scenario under analysis. These variables represent quantity-related decisions, i.e., how much blood is collected in each type of collection unit, how much is transported to blood centres, how much is processed and produced, how much is distributed to demand nodes, how much is wasted and how much is in short supply. All variables are presented below, duly described.

Binary variables

Y_{jq_j}	1 if a fixed blood collection unit is established at location j with capacity level q_j; 0 otherwise
Y'_{kq_k}	1 if a blood centre is established at location k with capacity level q_k; 0 otherwise
Z_{ij}	1 if donor group i is assigned to the fixed blood collection unit j; 0 otherwise
Z'_{in}	1 if donor group i is assigned to the mobile blood collection unit n; 0 otherwise
Z''_{ik}	1 if donor group i is assigned to blood centre k; 0 otherwise
Z'''_{jk}	1 if the fixed blood collection unit j is assigned to blood centre k; 0 otherwise
Z''''_{nk}	1 if the mobile blood collection unit n is assigned to blood centre k; 0 otherwise
Z'''''_{hk}	1 if demand node h is assigned to blood centre k; 0 otherwise

Positive integer variables

V_{bmijts}	The amount of blood type b donated by donor group i by method m in fixed blood collection unit j during period t in scenario s
V'_{bmints}	The amount of blood type b donated by donor group i by method m in mobile blood collection unit n during period t in scenario s
V''_{bmikts}	The amount of blood type b donated by donor group i by method m in blood centre k during period t in scenario s
O_{bmjkts}	The amount of blood type b donated by method m and transported from the fixed blood collection unit j to blood centre k during period t in scenario s
O'_{bmnkts}	The amount of blood type b donated by method m and transported from the mobile blood collection unit n to blood centre k during period t in scenario s
Q_{pbmkts}	The amount of blood product p of type b donated by method m and produced in blood centre k during period t in scenario s
G_{pbkts}	The amount of blood product p of type b produced in blood centre k during period t in scenario s
$U_{pb'bkhts}$	The amount of blood product p of type b distributed from blood centre k to demand node h during period t in scenario s to meet the demand for type b'
W_{pbkts}	The amount of blood product p of type b that is wasted in blood centre k during period t in scenario s
W'_{pbhts}	The amount of blood product p of type b that is wasted at demand node h during period t in scenario s
R_{pbhts}	The amount of blood product p of type b in shortage at demand node h during period t in scenario s

3.2.3. Objective functions

The optimisation model presents a single objective function that is intended to be minimised. However, this is composed of several terms – the cost of establishing blood facilities ($EstC$), the operational cost of collection (OpC), the transportation cost ($TranspoC$), the inventory storage cost ($InvC$), the production cost ($ProdC$), the substitution cost between blood types ($SubC$), the shortage

cost ($StgC$), the wastage cost ($WstC$) and the environmental penalty due to carbon emissions associated with the network's transport activities ($EnvC$).

$$Minimise\ Z_1 = EstC + OpC + TranspoC + InvC + ProdC + SubC + StgC + WstC + EnvC \quad (1)$$

$$EstC = \sum_j \left(f_{jq_j} + e_{jq_j}\right) \times Y_{jq_j} + \sum_k \left(f'_{kq_k} + e'_{kq_k}\right) \times Y'_{kq_k} \quad (1a)$$

$$OpC = \left(\sum_b \sum_m \sum_i \sum_j \sum_t \sum_s V_{bmijts} + \sum_b \sum_m \sum_i \sum_n \sum_t \sum_s V'_{b"WB"ints} + \sum_b \sum_m \sum_i \sum_k \sum_t \sum_s V''_{bmikts}\right) \times oc_m \times \pi_s \quad (1b)$$

$$TranspoC = \left(\sum_b \sum_m \sum_j \sum_k \sum_t \sum_s tc_{jk} \times O_{bmjkts} + \sum_b \sum_m \sum_n \sum_k \sum_t \sum_s tc'_{nk} \times O'_{bmnkts} + \sum_k \sum_{b\prime} \sum_b \sum_h \sum_p \sum_t \sum_s tc''_{kh} \times U_{pb\prime bkhts}\right) \times \pi_s \quad (1c)$$

$$InvC = \left(\sum_p \sum_b \sum_k \sum_t \sum_s ic_{pk} \times G_{pbkts} + \sum_p \sum_{b\prime} \sum_b \sum_k \sum_h \sum_t \sum_s ic'_{ph} \times U_{pb\prime bkhts}\right) \times \pi_s \quad (1d)$$

$$ProdC = \sum_p \sum_b \sum_m \sum_k \sum_t \sum_s pc_{pm} \times Q_{pbmkts} \times \pi_s \quad (1e)$$

$$SubC = \sum_p \sum_{b\prime} \sum_b \sum_k \sum_h \sum_t \sum_s U_{pb\prime bkhts} \times \nabla_{bb\prime} \times sc_{bb\prime} \times \pi_s \quad (1f)$$

$$StgC = \sum_p \sum_b \sum_h \sum_t \sum_s R_{pbhts} \times stg_p \times \pi_s \quad (1g)$$

$$WstC = \left(\sum_p \sum_b \sum_k \sum_t \sum_s W_{pbkts} + \sum_p \sum_b \sum_h \sum_t \sum_s W'_{pbhts}\right) \times wst_p \times \pi_s \quad (1h)$$

$$EnvC = \left(\sum_b \sum_m \sum_j \sum_k \sum_t \sum_s ce_{jk} \times \partial'''_{jk} \times O_{bmjkts} + \sum_b \sum_m \sum_n \sum_k \sum_t \sum_s ce'_{nk} \times \partial''''_{nk} \times O'_{bmnkts} + \sum_p \sum_{b\prime} \sum_b \sum_k \sum_h \sum_t \sum_s ce''_{kh} \times \partial'''''_{hk} \times U_{pb\prime bkhts}\right) \times co_2 c \times \pi_s \quad (1i)$$

The cost of establishing blood facilities is introduced in equation (1a) and consists of two terms – the first concerns fixed blood collection units and the second blood centres. It should also be noted that both terms include two separate cost parameters – one relating to the cost of physically establishing the

blood facilities and the other relating to the cost of properly equipping them. These parameters are then multiplied by the binary variable that determines whether or not the blood facilities are to be opened.

The operational cost of collection is presented in equation (1b) and results from multiplying the quantities collected in fixed and mobile blood collection units and blood centres by the operational cost of donation, which depends on the collection method employed. In addition, it is necessary to multiply by the probability of occurrence of scenario s, since the variables in the equation are impacted by the values taken by the uncertain parameters.

The cost of transportation in the BSC network is presented in equation (1c), which includes three components. The first two refer to the shipment of donations collected in fixed and mobile blood collection units to blood centres, and the third to the distribution of blood products from blood centres to demand nodes. All components result from multiplying the unit transportation cost by the number of donations or blood products transported in each case. Additionally, this is multiplied by the probability of occurrence of scenario s, since the variables in the equation are subject to the realisation of uncertainty.

The total cost of blood inventory is presented in equation (1d), consisting of two terms. The first term refers to the storage of blood products in blood centres and the second to pre-transfusion storage, which occurs in demand nodes. After processing, all blood products are stored according to their specific temperature conditions, so the cost of keeping them in inventory results from multiplying the unit cost of storage by the total quantity produced. Regarding the inventory in demand nodes, the total cost results from multiplying the unit cost of storage by the total amount received by the demand node, since all blood products must be properly refrigerated until the moment of their transfusion. Similar to the previous equations, this also needs to be multiplied by the probability of occurrence of scenario s.

Equation (1e) determines the total cost of production. The cost of processing donations depends on the collection method and the blood product to be produced. Therefore, the total production cost is derived as a result of multiplying the unit production cost by the total amount produced in each scenario and the probability of that scenario s.

The total cost of substituting blood products from a shortage blood type with a compatible blood type is determined by equation (1f). Substitutability between blood types is not medically desirable and therefore this cost is a penalty aimed at minimising substitutions. Furthermore, not all substitutions are equally favourable, so the ABO group substitution priority matrix worsens the cost of certain substitutions. Thus, the cost of substitution between blood types results from multiplying the quantity of each blood product of each type that is distributed to the demand nodes by the priority matrix and by the unit cost of substitution. Since the quantity distributed depends on the values taken by the uncertain parameters, it is necessary to further multiply by the probability of occurrence of scenario s.

When the substitution of a sought-after blood type with a compatible one is not possible, a shortage exists. Equation (1g) provides the shortage cost, which results from multiplying the total quantity in deficit in demand nodes by the unit cost of shortage of each blood product. The shortage quantity depends not only on demand but also on supply, since the latter drives the quantity produced. Thus, the shortage cost is also multiplied by the probability of occurrence of scenario s. Since shortages are highly

undesirable, as they compromise the quality of the service provided, this term of the objective function represents a penalty aimed at discouraging shortages.

On the other hand, wastage of blood products also entails costs. The cost of wastage is presented in equation (1h) and results from multiplying the total amount wasted, both in blood centres and in demand nodes, by the unit cost of wastage for each type of blood product. This unit cost therefore reflects the cost incurred in the collection of the donation that yielded the product, the cost of processing and subsequent storage. Wastage is considered to occur in blood centres when the quantity produced exceeds the quantity dispatched and, in the case of demand nodes, when the quantity received in each period exceeds the observed demand. The equation is further multiplied by the probability of occurrence of scenario s, since wasted quantities are sensitive to uncertainty.

Finally, equation (1i) estimates the cost of carbon emissions from the transport activities, being composed of three terms. All terms result from multiplying carbon emission rates by the distances travelled and the quantities transported in each process – shipment and distribution. The first and second term refer to the transportation of donations collected in fixed and mobile blood collection units, respectively, to blood centres and the third term refers to the distribution of blood products from blood centres to demand nodes. All these terms are further multiplied by the carbon price, so as to penalize emissions, and by the probability of occurrence of scenario s, since the values of the variables concerned depend on the realisation of the uncertainty of parameters such as supply and demand.

3.2.4. Model constraints

This subsection introduces the model constraints to which the objective function is subject to. The constraints are grouped by theme, given the specifics of the problem, and their scope is made explicit.

Assignment constraints

$$\sum_{q_j} Y_{jq_j} \leq 1, \forall\, j \tag{2}$$

$$\sum_{q_k} Y'_{kq_k} \leq 1, \forall\, k \tag{3}$$

$$Z_{ij} \leq \sum_{q_j} Y_{jq_j}\ , \forall\, i, j \tag{4}$$

$$Z''_{ik} \leq \sum_{q_k} Y'_{kq_k}\ , \forall\, i, k \tag{5}$$

$$Z'''_{jk} \leq \sum_{q_k} Y'_{kq_k}\ , \forall\, j, k \tag{6}$$

$$\sum_{k} Z'''_{jk} \leq 1, \forall\, j \tag{7}$$

$$Z''''_{nk} \leq \sum_{q_k} Y'_{kq_k}\ , \forall\, n, k \tag{8}$$

$$\sum_{k} Z''''_{nk} \leq 1, \forall\, n \tag{9}$$

$$Z''''''_{hk} \leq \sum_{q_k} Y'_{kq_k} \ , \forall\, h,k \tag{10}$$

$$\sum_{k} Z''''''_{hk} \leq 1, \forall\, h \tag{11}$$

The first group of constraints are the assignment constraints. These concern decisions on the establishment of blood facilities and on the allocation of donors to collection units and demand nodes to blood centres. Specifically, constraint (2) states that at most one fixed blood collection unit may be established at each location j with capacity level q_j; constraint (3) states that at most one blood centre may be established in each location k with capacity level q_k; constraint (4) states that each donor group i may only be assigned to a fixed blood collection unit j with capacity level q_j that is established; constraint (5) states that each donor group i may only be assigned to a blood centre k with capacity level q_k that is established; constraint (6) states that each fixed blood collection unit j may only be assigned to a blood centre k with capacity level q_k that is established; constraint (7) states that any fixed blood collection unit j may only be assigned to at most one blood centre k; constraint (8) states that each mobile blood collection unit n may only be assigned to a blood centre k with capacity level q_k that is established; constraint (9) states that any mobile blood collection unit n may only be assigned to at most one blood centre k; constraint (10) states that each demand node h may only be assigned to a blood centre k with capacity level q_k that is established; and finally, constraint (11) states that any demand node h may only be assigned to at most one blood centre k.

Constraints on distances

$$\partial_{ij} \times Z_{ij} \leq mdc, \forall\, i,j \tag{12}$$

$$\partial'_{in} \times Z'_{in} \leq mdc, \forall\, i,n \tag{13}$$

$$\partial''_{ik} \times Z''_{ik} \leq mdc, \forall\, i,k \tag{14}$$

$$\partial'''_{jk} \times Z'''_{jk} \leq mdp, \forall\, j,k \tag{15}$$

$$\partial''''_{nk} \times Z''''_{nk} \leq mdp, \forall\, n,k \tag{16}$$

$$\partial'''''_{hk} \times Z'''''_{hk} \leq mdd, \forall\, h,k \tag{17}$$

The second group of constraints are distance constraints between donor groups and blood collection facilities and between different blood facilities in the SC. Specifically, constraints (12) and (13) state that the distance between donor group i and the fixed and mobile blood collection units j and n, respectively, to which it is assigned should not exceed the maximum distance stipulated for collection – mdc; similarly, constraint (14) states that the distance between donor group i and the blood centre k to which it is assigned should not exceed the maximum distance stipulated for collection – mdc; constraint (15) states that the distance between the fixed blood collection unit located in j and the blood centre located in k to which it is assigned should not exceed the maximum distance stipulated for processing – mdp; similarly to the former, constraint (16) states that the distance between the mobile blood collection unit located in n and the blood centre located in k to which it is assigned should also not exceed the maximum distance stipulated for processing – mdp; and finally, constraint (17) states that the distance between demand node h and the blood centre located in k to which it is assigned should not exceed the maximum distance stipulated for distribution – mdd.

The existence of a maximum distance between each group of donors and the fixed blood collection units, mobile blood collection units and blood centres is socially motivated and aims to ensure that all donors can access the collection facilities within a short travel time. Also, it should be noted that, given the assignment constraints, there is no limit on the number of collection facilities to which the same group of donors can be allocated. Donor groups may therefore donate in one or more collection facilities of the same type, provided these are located within the mdc. This is a measure that allows donor groups to have greater flexibility and choice, bringing the model closer to real collection practices.

The existence of a maximum distance between fixed and mobile blood collection units and blood centres is intended to ensure that collected donations are shipped as quickly as possible and without exceeding the processing time limit, which, according to the literature reviewed, is six hours. Finally, a maximum distance between demand nodes and blood centres is also defined so that the distribution of blood products is expeditious and they reach the demand nodes in their best conditions of freshness.

Constraints on collection sites

$$V_{bmijts} \leq \omega \times Z_{ij}, \forall\, b, m, i, j, t, s \tag{18}$$

$$V'_{b"WB"ints} \leq \omega \times Z'_{in}, \forall\, b, m, i, n, t, s \tag{19}$$

$$V''_{bmikts} \leq \omega \times Z''_{ik}, \forall\, b, m, i, k, t, s \tag{20}$$

The third group of constraints are the constraints on collection sites which provide that blood can only be collected from each group of donors in the collection facilities to which they are assigned. Specifically, constraints (18), (19) and (20) indicate that blood collection from each of the donor groups i is only possible in the fixed blood collection units j, the mobile blood collection units n and the blood centres k to which they are assigned, respectively.

Constraints on collection, production and storage capacity

$$\sum_b \sum_m \sum_i V_{bmijts} \leq \sum_{q_j} ccap_{jq_j} \times Y_{jq_j}, \forall\, j, t, s \tag{21}$$

$$\sum_b \sum_m \sum_i V'_{b"WB"ints} \leq ccap'_n, \forall\, n, t, s \tag{22}$$

$$\sum_b \sum_m \sum_i V''_{bmikts} \leq \sum_{q_k} ccap''_{kq_k} \times Y'_{kq_k}, \forall\, k, t, s \tag{23}$$

$$\sum_b G_{pbkts} \leq \sum_{q_k} pcap_{pkq_k} \times Y'_{kq_k}, \forall\, p, k, t, s \tag{24}$$

$$\sum_b G_{pbkts} \leq \sum_{q_k} scap_{pkq_k} \times Y'_{kq_k}, \forall\, p, k, t, s \tag{25}$$

$$\sum_{b'} \sum_b \sum_k U_{pb'bkhts} \leq scap'_{ph}, \forall\, p, h, t, s \tag{26}$$

The fourth group of constraints ensures that the capacity of the facilities in the BSC is not exceeded, whether this concerns collection, production or storage capacity. Specifically, constraint (21) states that the total amount of blood collected in each fixed blood collection unit j with capacity level q_j in each period t should not exceed its collection capacity; constraint (22) states that the total amount of blood collected in each mobile blood collection unit n in each period t must not exceed its collection capacity;

constraint (23) states that the total amount of blood collected in each blood centre k with capacity level q_k in each period t should not exceed its collection capacity; constraint (24) states that the production of any blood product p in blood centre k in each period t should not exceed the production capacity that the blood centre concerned has available for such product; constraint (25) states that the production of any blood product p in blood centre k in each period t should not exceed the storage capacity that the blood centre concerned has available for such product; constraint (26) states that the amount of any blood product p arriving at any hospital h in each period t should not exceed its storage capacity.

Constraint on supply capacity

$$\sum_{m}\sum_{j} V_{bmijts} + \sum_{m}\sum_{n} V'_{b"WB"ints} + \sum_{m}\sum_{k} V''_{bmikts} \leq s_{bits}, \forall\, b, i, t, s \tag{27}$$

The fifth group of constraints includes only constraint (27), which concerns the donors' capacity to supply blood. It states that in each period t, the total amount of blood type b collected from donor group i in all fixed blood collection units j, mobile blood collection units n, and blood centres k, through all collection methods m, must not exceed the maximum supply capacity of the donor group concerned.

Constraints on donations shipment

$$O_{bmjkts} \leq \omega \times Z'''_{jk}, \forall\, b, m, j, k, t, s \tag{28}$$

$$O'_{bmnkts} \leq \omega \times Z''''_{nk}, \forall\, b, m, n, k, t, s \tag{29}$$

$$\sum_{i} V_{bmijts} \sum_{k} O_{bmjkts}, \forall\, b, m, j, t, s \tag{30}$$

$$\sum_{i} V'_{b"WB"ints} = \sum_{k} O'_{bmnkts}, \forall\, b, m, n, t, s \tag{31}$$

The sixth group of constraints concerns the shipment of donations to blood centres. Specifically, constraints (28) and (29) state that shipments of blood donations from fixed blood collection units j and mobile blood collection units n, respectively, are only possible to the blood centres k to which they are assigned. Constraints (30) and (31) introduce flow conservation for donations collected in fixed and mobile blood collection units, respectively. That is, there is no storage of inventory in collection units, and therefore all donations from fixed blood collection units j and mobile blood collection units n should be shipped to blood centres k.

Production constraints

$$\varphi_m \times \delta_{pm} \times \left(\sum_{j} O_{bmjkts} + \sum_{n} O'_{bmnkts} + \sum_{i} V''_{bmikts} \right) = Q_{pbmkts}, \forall\, p, b, m, k, t, s \tag{32}$$

$$\sum_{m} Q_{pbmkts} = G_{pbkts}, \forall\, p, b, k, t, s \tag{33}$$

The seventh group of constraints concerns production, namely the quantity produced of each blood product. Constraint (32) establishes the relationship between the donations collected and the resulting blood products after processing. As not all donations meet the requirements to be processed, the percentage of their use needs to be taken into account. Moreover, not all donations have the potential to produce the same variety and amount of blood products, which depends on the method of collection

by which they were obtained. Therefore, to determine the quantity of each blood product produced, it is necessary to multiply both the utilisation rate and the production rate by the total quantity of donations arriving at the blood centre. The quantity to be processed in the blood centre is that which comes from all the fixed and mobile blood collection units assigned to it together with the quantity collected in the concerned blood centre. Constraint (33) implies an equilibrium relationship in production. That is, the amount of blood product p of type b produced in blood centre k in each period t should equal the total amount of that same blood product produced in the blood centre and period concerned from donations collected by all available collection methods m.

Constraints on blood product distribution

$$G_{pbkts} = \sum_{b\prime} \sum_{h} U_{pb\prime bkhts} \times \Delta_{bb\prime} + W_{pbkts}, \forall\, p, b, k, t, s \tag{34}$$

$$\sum_{b} \sum_{k} U_{pb\prime bkhts} \times \Delta_{bb\prime} = dem_{pb\prime hts} + W'_{pb\prime hts} - R_{pb\prime hts}, \forall\, p, b', h, t, s \tag{35}$$

$$\sum_{p} \sum_{b\prime} \sum_{b} U_{pb\prime bkhts} \leq \omega \times Z''''_{hk}, \forall\, h, k, t, s \tag{36}$$

The eighth group of constraints concerns the quantity of each blood product that is distributed from the blood centres to meet demand. Constraint (34) represents the conservation of blood product flow in blood centres. That is, the total amount of a blood product p of type b produced in a blood centre k in each period t must equal the amount of that product that is distributed from that blood centre to all demand nodes h in that period, together with the amount that is wasted, if any. Constraint (35) aims at satisfying demand, although shortage is admitted. That is, it imposes that the quantity of each blood product p to be distributed from all blood centres k to demand node h, in any period t, is always equal to the demand experienced by that demand node in such period together with wastage or shortage quantity. It should be noted that the term on the left assumes that there can be substitutability between blood types, which occurs when the blood centre does not hold enough blood product p of type b' and ships the required product but of type b. Finally, constraint (36) states that the distribution of blood products from blood centres k can only occur to the demand nodes h that are allocated to them.

Constraints on the domain of variables

$$Y_j, Y'_k, Z_{ij}, Z'_{in}, Z''_{ik}, Z'''_{jk}, Z''''_{nk}, Z'''''_{hk} \in \{0, 1\} \tag{37}$$

$$V_{bmijts}, V'_{bmints}, V''_{bmikts}, O_{bmjkts}, O'_{bmnkts}, Q_{pbmkts}, G_{pbkts}, U_{pb\prime bkhts}, W_{pbkts}, W'_{pbhts}, R_{pbhts} \geq 0, \forall\, b, b', m, i, j, n, k, p, h, t, s \tag{38}$$

Finally, the constraints on the domain of variables are presented, with constraint (37) concerning binary variables and constraint (38) concerning positive integer variables.

3.3. Chapter conclusions

In this third chapter the problem was formally stated. However, the focus is placed on the optimisation model presented. It is intended to assist in decision making regarding the location and capacity of the blood facilities to be established and the various allocation decisions, and therefore fits into the tactical-strategic planning. The mathematical approach adopted to cope with demand and

supply uncertainty resorts to two-stage stochastic programming and is therefore scenario-based. The solution approach, in turn, conforms to exact methods given that the model is a mixed integer linear programming model. The main features of the model, which provide added value to the existing literature, are that it simultaneously combines economic, wastage reduction, environmental, social and blood group substitutability concerns. However, since it is a tactical-strategic model, whose planning horizon aims at the medium and long term, some assumptions are imposed. Among these, it is worth highlighting that the transition of blood product inventory between periods is not taken into account and, therefore, perishability is also neglected in the model.

In order to apply the model to a real example, the Portuguese BSC is presented next. Thus, Chapter 4 describes the case study, which includes an analysis of the performance of this SC in order to identify its main inefficiencies.

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

This chapter aims to present the blood scene in Portugal and is divided into three sections. Section 4.1. refers to the entity responsible for the management and regulation of all blood-related activities, the IPST, and is subdivided into three subsections. Subsection 4.1.1. presents the history and organisational structure of IPST. Next, Subsection 4.1.2. describes the Portuguese BSC. Having understood its constitution and functioning, its performance is analysed in Subsection 4.1.3. This analysis is supported by recent operational activity data. Section 4.2. follows from the previous analysis and specifies the main inefficiencies of the Portuguese BSC. Finally, Section 4.3. presents the chapter's conclusions.

4.1. Instituto Português do Sangue e da Transplantação, IP

4.1.1. Historical context and organisational structure

The origin of an entity responsible for collection, production, inventory and distribution of blood products in Portugal dates back to the 1950s (IPST, 2020). At that time the volume of blood products available was clearly insufficient to meet the needs, resulting in competition in demand and excessively high trading prices. To address this problem, a public entity that aimed to ensure a balance between supply and demand was established in 1958, the Instituto Nacional do Sangue. The corresponding decree-law envisaged three delegations, in Lisboa, Porto and Coimbra, and sub-delegations in unspecified regional hospitals (Diário da República Eletrónico, 2021). Later, in the 1980s, therapeutic advances in healthcare changed the transfusion paradigm in Portugal which resulted in shortages once again, exposing the fragilities of the Instituto Nacional do Sangue. It was then, in the 1990s, that the Instituto Nacional do Sangue was restructured and renamed Instituto Português do Sangue. The Instituto Português do Sangue was an autonomous public entity under the tutelage of the Government and its purpose was to effectively coordinate and regulate all facilities in the existing BSC. This institution consisted of the three previous delegations, called Centros Regionais de Sangue, responsible for the BSC processes from collection to distribution, and the immunohematotherapy services in healthcare facilities, responsible only for collection and production (IPST, 2020). In 2012 there was a new restructuring that consisted of the merger of Instituto Português do Sangue with other entities that operated in the areas of histocompatibility and transplantation, resulting in IPST (J. P. A. Sousa & Marques, 2019). IPST is currently a public organism endowed with autonomy and supervised by the Ministry of Health. Its mission is to ensure national self-sufficiency in terms of blood products, organs, tissues and human cells (Escoval & Marques, 2020a). In addition, IPST is a member of the European Blood Alliance, a non-profit association that brings together the national blood institutes of the member states of the European Union and the European Free Trade Association whose donation is voluntary and unpaid (European Blood Alliance, 2021).

As regards the organisational structure, IPST is essentially composed of national administrative divisions, which are coordinations, offices and departments, and territorially decentralised services (Escoval & Marques, 2020a). These correspond to the former Centros Regionais de Sangue, which after the final 2012 restructuring were renamed Centros de Sangue e da Transplantação (CSTs). The

geographical area of operation of each of these is distinct, but together they ensure the availability of blood products to the entire territory of mainland Portugal. Specifically, the Centro de Sangue e da Transplantação do Porto (CSTP) covers the Northern region, the Centro de Sangue e da Transplantação de Coimbra (CSTC) covers the Central region and the Centro de Sangue e da Transplantação de Lisboa (CSTL) covers the Lisboa e Vale do Tejo, Alentejo and Algarve regions, as illustrated in Figure 7 (J. P. A. Sousa & Sousa, 2017). Besides the distinction between national administrative divisions and territorially decentralised services, the IPST is further divided into two functional areas – blood and transplantation. These are transversal to the activity of any healthcare facility and therefore support the national health system (Escoval & Marques, 2020a). Given that the focus of this work is the BSC, only the blood functional area will be addressed hereafter. The organisational charts of the IPST and the CSTs are presented in Appendix B, in figures B1 and B2, respectively.

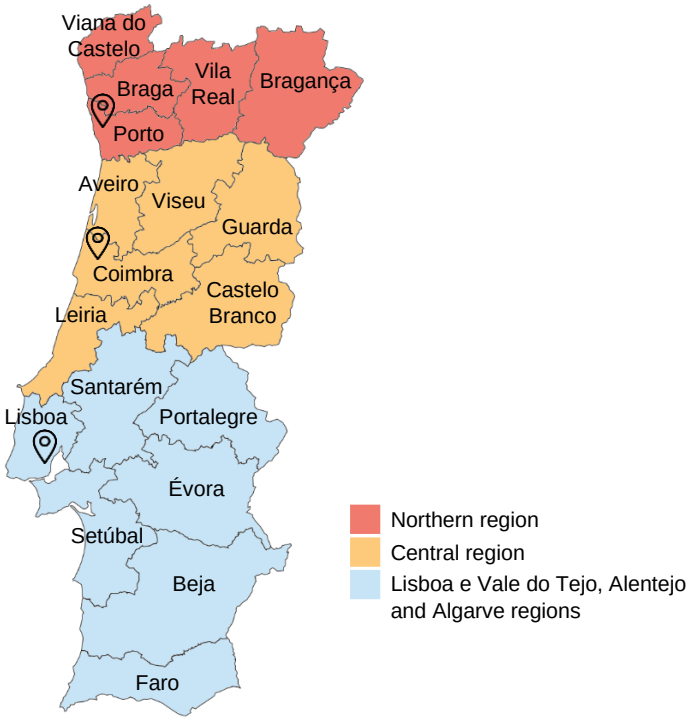

Figure 7 - Regions of operation of the CSTs

4.1.2. The Portuguese blood supply chain

The Portuguese BSC is composed of the three CSTs and 25 hospital blood units scattered throughout the national territory. The CSTs are responsible for the collection, separation into components, laboratory studies, storage and distribution of blood products. Furthermore, these are responsible for the articulation of blood product flows with demand nodes in their region, both public and private (Escoval & Marques, 2020a). Hospital blood units refer to healthcare facilities qualified to collect blood donations. The 25 hospital blood units that perform blood collection in Portugal are listed in Table C1 in Appendix C. Of these, seven are located in the Northern region, three in the Central region, eight in the Lisboa e Vale do Tejo region, five in the Alentejo region and two in the Algarve region (Escoval et al., 2020). As public information on their activities is scarce, it is not possible to fully identify which of these 25 carry out donation testing and processing. Still, it is known that there are at least four hospital

blood units in the Lisboa e Vale do Tejo region and two in the Alentejo region that perform testing and processing (Araújo et al., 2020). The blood-related activities of all hospital blood units are regulated by the IPST. Although the CSTs have a certain degree of autonomy, it is the IPST's directive council (*Conselho Diretivo*) that approves the activity plans and resources required for their implementation, which are proposed by the technical directors (*Direção Técnica*) of each CST. Therefore, although geographically dispersed, the CSTs are coordinated by IPST's top management, on which they are hierarchically dependent (J. P. A. Sousa & Sousa, 2017). In fact, the Portuguese BSC tends to be decentralised from a functional point of view but has a centralised structure in the transversal areas (Escoval & Marques, 2020a).

Regarding the collection process, it can take place in the CSTs, hospital blood units, mobile venues and bloodmobiles. In the case of CSTs, all are equipped to perform WB and apheresis collection (J. P. A. Sousa & Sousa, 2017). The donor may come to one of these facilities at any time and donate or may be contacted by them and invited to donate blood. Also, there is a wide range of hospital blood units in Portugal that perform blood collection procedures in the same way as the CSTs. In the case of mobile venues, the collections are limited to WB. The mobile venues are usually included in the annual activity plan of each CST and the collection sessions are organised in partnership with donor associations or local authority bodies. In addition, collection at mobile venues may be carried out on the own initiative of other organisations, such as companies or cultural associations. In these situations, the organisations contact the nearest CST, so that the latter can ascertain the physical conditions of the proposed space, plan and schedule the collection session. Specifically, the proposed space should be easily accessible to donors, ventilated, large, well lit, have sanitary facilities, and also have the possibility of different areas to receive and identify donors, carry out the clinical evaluation, draw blood, and provide a post-donation meal. If the proposed space does not meet the necessary conditions, the session will take place in a bloodmobile, which is a little-used resource (IPST, 2021).

With regard to the transportation of the necessary material and the technical collection teams, IPST adopts a mixed system, i.e., it uses its fleet and rents vehicles from external entities (J. P. A. Sousa & Sousa, 2017). After collection, donations must be refrigerated and processed within the processing time limit, which implies that they arrive at the processing facilities no later than six hours after blood has been withdrawn from donors. Processing facilities are located within both CSTs and component laboratories of hospital blood units. Information about the shipment process in official IPST documents is lacking. However, it is plausible that it occurs in a similar way to the transportation of physical and human resources of the mobile venues. That is, if the duration of the collection session is less than six hours and the distance from the mobile venues or bloodmobiles allows for transportation to the nearest processing facility within the processing time limit, then the shipment can take place using the same vehicles that were used to travel to these sites, either from IPST's fleet or rented vehicles. In the case of long duration collection sessions or locations distant from the processing facilities, it is plausible that shipment takes place as described by Mobasher et al. (2015). This means that the different mobile venues or bloodmobiles are grouped into clusters according to their proximity to each other, and each cluster is visited by a vehicle that collects donations and transports them to the nearest processing facility in that region.

Once donations arrive at the processing facilities, a small sample is taken from each donation for laboratory testing and the remaining blood is processed. The tests currently performed on all donation samples collected in Portugal are for human immunodeficiency virus, hepatitis B, hepatitis C, *T. Pallidum*, the micro-organism that causes syphilis, and HTLV1/2, a virus that can trigger cancer. In addition to these, when risk factors are identified in the clinical evaluation before the blood withdrawal, such as travelling, other tests may be performed (Escoval et al., 2020). If there are positive tests, the processing facilities forward the respective samples to the CSTP, where the confirmatory tests are carried out (Escoval & Marques, 2020a). Information in official IPST documents is very scarce and the specifics of processing are not known. According to the Optimal Blood Use Project (2010), Portugal follows the European trend of fractioning all or practically all WB donations into components. The blood components processed in larger quantities are RBC concentrates, followed by PLT concentrates, plasma and, finally, cryo (Escoval et al., 2020). In all these blood products, the removal of white blood cells is mandatory (Optimal Blood Use Project, 2010).

Once processing is complete, the resulting blood products are stored in the CSTs or hospital blood banks according to their specific refrigeration conditions. The blood products are thus kept in inventory until they are shipped to demand nodes, in the case of storage in CSTs, or until they are required for transfusion, in the case of storage in hospital blood banks. Should blood products exceed their shelf life in either of these facilities, they are discarded. Information on inventory management is also scarce. It is plausible to assume that the review period is a 1-day period in both CSTs and demand nodes, as considered by Osorio et al. (2017). Besides this, the issuing policy adopted was not found. Based on the literature review, it would be inferred that it is First In, First Out, since it is the one that entails the least wastage and is therefore the most efficient. The quantities of each blood product and for each type of blood kept in inventory will depend on the average daily demand of the demand nodes served by the CST in each region. However, the periodicity associated with the placement of orders by demand nodes to the CSTs is not addressed in official IPST sources. In view of the above, it would be deduced that it is daily.

Finally, the available information on distribution is also scarce. According to IPST (2017), daily lateral transhipment operations take place between the three CSTs and temperature-controlled transport is done exclusively through external contracting. Plasma, for example, must be transported at −25ºC and IPST does not own any vehicle with the specific conditions required.

4.1.3. Performance of the Portuguese blood supply chain

According to IPST, both the quantity of donations and the number of donors have been decreasing year after year, as shown in Figure 8 (Escoval et al., 2020). However, although the reduction in donations is in line with the international trend towards less use of blood products, it is below what is desirable and is therefore worrying, as is the reduction in the number of donors (Escoval & Marques, 2020c). IPST estimates that 35 donations per 1,000 inhabitants, evenly distributed throughout the year, are needed to meet the country's needs (J. P. A. Sousa & Sousa, 2017). However, besides the fact that blood donations are highly asymmetric on a weekly basis and seasonal, the ratio of donations per 1,000 inhabitants has decreased considerably in recent years (Escoval et al., 2020; Escoval & Marques,

2020c). Specifically, in 2011 it was 41.09, but since 2015 it has been below the desired value. According to the most recent information, in 2019 it stood at 31.03, indicating that the needs in blood products have not always been ensured (Escoval et al., 2020).

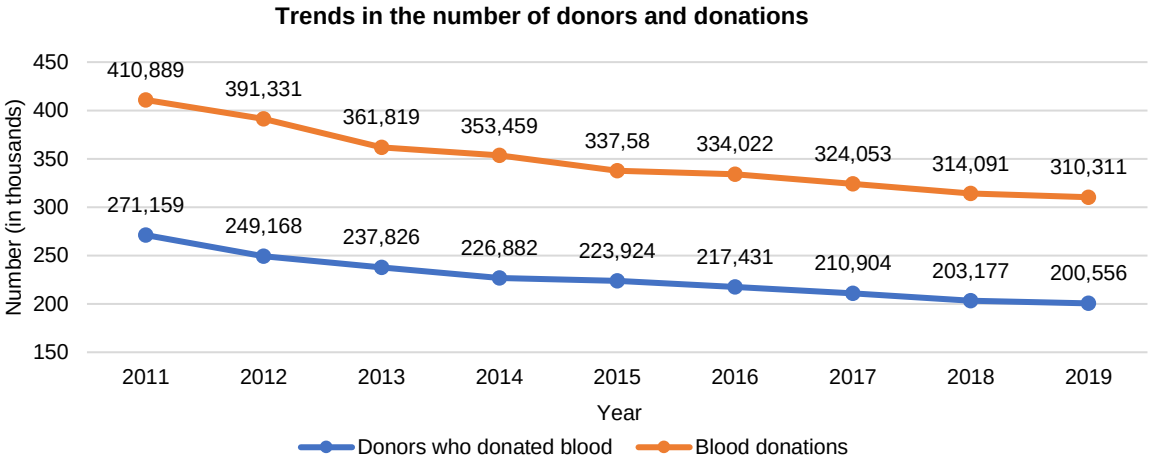

Figure 8 - Trends in the number of donors and donations. Source: Escoval et al. (2020)

In addition to the number of donors per 1,000 inhabitants, the number of new donors has also declined in recent years, which may trigger a supply problem in the future, compromising the balance of the BSC. According to the latest available data, in the year 2019, 310,311 blood donations were collected from 200,556 donors. Of these donations, 57.24% were collected by IPST at CSTs, mobile venues and bloodmobiles. The remaining 42.76% were collected in hospital blood units. These values have remained practically constant in recent years, which is evidence of the current importance of hospital-based collections. Considering the donations collected by IPST, 73.83% are collected in mobile venues, which implies a lot of travel and many physical and human resources (Escoval et al., 2020). However, in 2019 it was observed that there has been less willingness of donors to visit mobile venues. In this sense, the IPST identified the need to increase the collection sessions of this type, in order to bring them closer to the populations, minimising the distance that each donor would have to travel to donate blood (Escoval & Marques, 2020c). It is also noted that the overwhelming majority of donations, around 98%, are WB donations. Concerning apheresis, PLTs are the blood component obtained most often by this method (Escoval et al., 2020). According to Strategic Plan 2020 – 2022, one of the measures to be implemented is the adequacy of blood/components collection to consumption, which can be achieved by increasing the number of apheresis procedures (Escoval & Marques, 2020b). In fact, obtaining the most sought-after blood components through apheresis is a very efficient practice that could have a positive impact on wastage, although outdating is the most frequent cause of discard. The wastage due to outdating may indicate that there is inappropriate management of demand and supply. In addition, wastage may be enhanced by the need to stock a greater quantity of blood products than would correspond to planned needs, in order to cope with unforeseen medical emergencies (Escoval et al., 2020).

Table 3 presents the wastage associated with the main blood products in 2019, the most recent data available, this being measured as the difference between units produced and units transfused. Plasma and cryo are not considered in the analysis because they have a shelf life of 1 year and therefore

there are units produced in a given year that may only be transfused the following year. As such, these blood products are not always good indicators of wastage. Among the data presented, the wastage of PLT pool with pathogen reduction stands out, with more than one-fifth of the units produced being wasted. Still, this is not the most unused blood product. The wastage of PLTs produced from a unit of WB is over 50%, this figure being of great concern. In order to understand the overall trend, it is important to analyse data from previous years. However, past wastage was even more significant. Specifically, in 2018 it stood at 64.8%, in 2017 at 65.2% and in 2016 at 78.9%, which is evidence of a downward trend, albeit not very significant (Escoval et al., 2018, 2019; G. de Sousa et al., 2017).

Table 3 - Production, transfusion and wastage data by blood product for 2019. Source: Escoval et al. (2020)

Blood product	Units produced	Units transfused	Wastage	
			Absolute value	%
RBC concentrate	297,693	293,892	3,801	1.28
PLT pool (without pathogen reduction[4])	29,064	27,138	1,926	6.63
PLTs from a unit of WB	19,833	8,498	11,335	57.15
PLT pool (with pathogen reduction)	9,987	7,885	2,102	21.05

4.2. Problem characterisation

The data presented above on the performance of the BSC in Portugal suggests that it has inefficiencies. These inefficiencies are mainly associated with collection and transfusion, resulting in significant wastage. The 2019 data on the distribution of donations at the national level show that there is a marked asymmetry in the donation by region and by hospital blood units. Table 4 shows the donations collected by region. The North region stands out, contributing nearly 20% of the total national donations, a figure similar to the total donations collected in the Centre, Lisboa e Vale do Tejo, Alentejo and Algarve regions. Furthermore, there is a significant number of hospital blood units (17) whose annual donations are less than 5,000. In fact, of these, five performed less than 1,000 collections per year. Data from previous years are in line with those of 2019, indicating that the asymmetry observed in collections has been repeated over time.

There are also asymmetries between regions in terms of transfusions. The available data on transfusion distribution at the national level refers only to RBC concentrates. Thus, the following analysis is based only on this blood product. In fact, it is observed that the RBC concentrate is the most demanded blood product, being the one that presents the highest number of transfusions and the lowest wastage. Table 4 also shows the units of RBC concentrates transfused by region. It can be seen that this blood product is more demanded in the Lisboa e Vale do Tejo region, followed by the North and Centre regions, respectively. Regarding the Lisboa e Vale do Tejo region, it should be noted that transfusions were performed with units coming from other regions of the country, which was also the case in previous years. This situation shows the region's inability to meet its needs. Furthermore, in about 47% of the Portuguese demand nodes, less than one transfusion per day was administered and 22% did not perform any transfusion in 2019. Specifically, 24 demand nodes in the Lisboa e Vale do Tejo region and 20 in the Northern region did not transfuse RBC concentrates in 2019 (Escoval et al.,

[4] Pathogen reduction is a technique that results in the inactivation of microorganisms such as virus and bacteria that can cause disease in the recipient (Leitão, 2020)

2020). Thus, it can be seen that there are also considerable asymmetries with regard to transfusion at demand nodes. To the above facts, which expose a clear imbalance between demand and supply, especially in the Lisboa e Vale do Tejo region, it should be added that the IPST acknowledges, in the Strategic Plan 2017 – 2019, that the location of the CSTs was done in an unplanned way, with the two largest buildings (CSTC and CSTP) located in the north of the country and more than 100 kilometres (km) apart (J. P. A. Sousa & Sousa, 2017). Thus, the regional distribution of the CSTs contributes to the asymmetries found and, consequently, to the inefficient performance of the Portuguese BSC. In this sense, the SCND presents itself as an area of study that may contribute positively to reduce or eliminate the asymmetries identified, through the redesign of the existing network.

Table 4 - Donations and transfusions of RBC concentrate by region in 2019. Source: Escoval et al. (2020)

IPST/Region	Donations		Transfusions of RBC concentrates	
	Absolute value	%	Absolute value	%
CSTC	48,338	15.58	–	–
CSTL	56,160	18.10	–	–
CSTP	73,123	23.56	–	–
Alentejo	12,311	3.97	11,551	3.93
Algarve	10,036	3.23	10,724	3.65
Centre	17,666	5.69	56,968	19.38
Island Portugal	9,423	3.04	9,705	3.30
Lisboa e Vale do Tejo	23,588	7.60	113,433	38.60
North	59,666	19.23	91,511	31.14

4.3. Chapter conclusions

This chapter presented the case study of the Portuguese BSC. The entity responsible for coordinating and regulating its activity is the IPST, so its historical context and organisational structure were introduced. Next, the functioning of the BSC was described, which is in line with what was previously explained in the literature review. That is, the Portuguese BSC has a centralised structure and the activities associated with the four echelons take place in the CSTs, which are similar to the blood centres mentioned in the previous chapter. Additionally, collection and production may also occur in hospital blood units. After the description of the BSC, its performance was analysed and it was concluded that there are blood products whose wastage is quite high, namely PLT pool (with pathogen reduction) and PLTs from a unit of WB. In order to understand the factors behind the observed wastage, data on collection and transfusion were analysed and it was concluded that there is an imbalance between demand and supply, which has been perpetuated over time. In this sense, the need arises to redesign the BSC network in Portugal, in order to correct the inefficiencies identified.

Next, Chapter 5 focuses on the data collection and treatment required to implement the model to the Portuguese case study. Specifically, it reveals the procedures adopted in constituting the various sets and obtaining the parameters. Also, the extrapolations and assumptions made are detailed.

5. Data collection and treatment for the Portugal Case Study

This chapter aims to describe the procedures followed in the research and treatment of the data required to implement the model previously presented. The chapter is divided into two sections. Section 5.1. presents the criteria followed in defining the composition of the various sets, duly justified. Section 5.2. is organised into seven subsections and presents the values of each parameter, the means by which they were obtained and the underlying assumptions. In the particular case of uncertain parameters, the data extrapolation process is detailed.

5.1. Set definition

Firstly, it should be noted that this study is limited to mainland Portugal. The territory is organised into districts and each of these into municipalities. To model the Portuguese BSC as accurately as possible, all districts should be considered as possible locations for the establishment of facilities. However, the size of the potential location sets, particularly I, J, K and N, would make the model very complex and excessively time-consuming to implement. Therefore, due to computational concerns, the size of each set has to be contained so that the model can produce reliable results on acceptable timescales. To that end, the population density of all municipalities that constitute the 18 districts of mainland Portugal was analysed. The results show that in six of these districts – Bragança, Guarda, Castelo Branco, Portalegre, Évora and Beja – there is no municipality whose population density is equal to or higher than the average for mainland Portugal, which is 109.9 inhabitants/km^2 (PORDATA, 2021). As such, it was decided to exclude these districts from the implementation of the model. Therefore, the remaining 12 districts considered are Viana do Castelo, Braga, Porto, Vila Real, Aveiro, Viseu, Coimbra, Leiria, Santarém, Lisboa, Setúbal and Faro.

Donor groups

For the donor groups, the municipality with the highest population density from each of the previous 12 districts considered was selected. The resulting locations are presented in Appendix D, listed in Table D1 and mapped in Figure D1. The choice of population density as a criterion is based on the assumption that more densely populated areas have greater donor potential.

Fixed blood collection units

The first step in deciding the composition of the fixed blood collection units set, J, was to find the current location of such existing facilities. In 2019, and according to Escoval et al. (2020), there were 25 fixed blood collection units, as in Table C1 in Appendix C. The existing facilities are located in 13 of the country's 18 districts – Beja, Braga, Castelo Branco, Coimbra, Évora, Faro, Lisboa, Portalegre, Porto, Santarém, Setúbal, Viana do Castelo e Viseu. Due to computational reasons, the locations of the 25 fixed blood collection units are not considered, but only the capitals of the districts in which these facilities are located, provided that these have at least one municipality with a population density equal or greater that the mainland average. This means that the districts of Beja, Castelo Branco, Évora and Portalegre are excluded. Contrarily, there is currently no fixed blood collection unit in the districts of Aveiro, Bragança, Guarda, Leiria and Vila Real. As in Bragança and Guarda all the municipalities have a population density below the average of mainland Portugal, only the municipality with the highest

population density in each of the districts of Aveiro, Leiria and Vila Real was selected as a candidate location. São João da Madeira was selected in the district of Aveiro, Peniche in the district of Leiria and Peso da Régua in the district of Vila Real. All the elements of set J are presented in Appendix D, listed in Table D1 and mapped in Figure D2.

Additionally, note that while some of the existing fixed blood collection units may be able to test and process donations, it is assumed that these processes are carried out exclusively by blood centres. Consequently, all fixed blood collection units have their operation restricted to collection.

Blood centres

With regard to the selection of the locations of the blood centre set, K, the decision was simple. From the 12 districts considered in the analysis, there are currently blood centres in three of these – Lisboa, Porto and Coimbra. The district capitals of the remaining nine more densely populated districts are selected as candidate locations. Existing and candidate locations for blood centres are presented in Appendix D, listed in Table D3 and mapped in Figure D3.

Mobile blood collection units

For the set of mobile blood collection units, N, a municipality was randomly selected from each of the 12 districts under analysis, using *Microsoft Excel*. The results obtained are presented in Appendix D, listed in Table D4 and mapped in Figure D4. The decision was made to randomly select municipalities rather than those with the highest population density because mobile blood collection units act as external donation supply points, representing the supply from mobile venues that usually travel throughout the country over time.

Capacity levels

The sets of capacity levels to be selected for fixed blood collection units and blood centres – Q_J and Q_K, respectively, include only two elements each. Thus, two capacity levels are available for each fixed blood collection unit $j - q_{j_1}$and q_{j_2}, and for each blood centre $k - q_{k_1}$ and q_{k_2}. Both for fixed blood collection units and blood centres, capacity level 1 represents the current capacity of the Portuguese BSC facilities and capacity level 2 represents a 25% increase in current capacity. The values of these capacities are presented in Subsection 5.2.2, which addresses capacity parameters.

Demand nodes

As for the demand nodes, H, the first step in selecting the elements of the set consisted in listing all hospitals of the National Health Service and identifying the municipality and district to which they belong. Next, the population density of these municipalities was analysed. For each of the 12 districts of mainland Portugal under analysis, the municipality with the highest population density in which there are public hospitals was identified. This analysis then resulted in the demand nodes presented in Appendix D, listed in Table D5 and mapped in Figure D5.

Blood donation methods

Although apheresis of several blood components is possible, only PLT apheresis donations are representative in Portugal. As such, the model considers WB and PLT apheresis as the sole collection methods. In 2019, for example, there were only two RBC apheresis donations (Escoval et al., 2020).

Blood products

As previously mentioned, four main blood products exist. Yet, only two are included in the model implementation – RBCs and PLTs. Plasma is excluded because, after it is obtained, usually several other by-products are extracted from it, and it is these plasma by-products that are then transfused. In the case of cryo, this is produced and demanded in very low quantity. Only 334 units were transfused in 2019, representing 0.085% of the total transfusions performed that year (Escoval et al., 2020).

Blood types

Within the blood types set, all eight existing are covered – AB+, AB–, A+, A–, B+, B–, O+ and O–.

Time planning periods

Given the tactical-strategic nature of the model, four time periods of six months each are considered, resulting in a planning horizon of two years. The length of each period was defined as Fattahi et al. (2017) consider that in SC planning problems, tactical periods should be longer than three months. Due to computational limitations, it is not possible to extend the study.

Scenarios

Finally, the set of scenarios, S, has nine elements, resulting from varying both uncertain parameters by +10% and -10%. Table 5 outlines the main features of each scenario.

Table 5 - Stochastic model scenarios

Scenario	Supply	Demand
S1	Estimated 2019 supply	Estimated 2019 demand
S2	Estimated 2019 supply	-10% of estimated 2019 demand
S3	Estimated 2019 supply	+10% of estimated 2019 demand
S4	-10% of estimated 2019 supply	Estimated 2019 demand
S5	-10% of estimated 2019 supply	-10% of estimated 2019 demand
S6	-10% of estimated 2019 supply	+10% of estimated 2019 demand
S7	+10% of estimated 2019 supply	Estimated 2019 demand
S8	+10% of estimated 2019 supply	-10% of estimated 2019 demand
S9	+10% of estimated 2019 supply	+10% of estimated 2019 demand

5.2. Parameters – data search and extrapolation

This section is divided into seven subsections. Each of these addresses the process of gathering and processing data to obtain the values for cost, capacity, distance, production, substitutability, environmental, uncertain and other parameters. It is worth highlighting Subsection 5.2.7, where the extrapolation processes followed in the case of supply and demand parameters are explained.

5.2.1. Cost parameters

Establishment and equipping costs of blood centres

Obtaining the cost parameters for the establishment and equipment of blood centres is an extremely challenging task. In the literature, there are very few articles that present this type of costs. Of those that do, the values are in currencies that do not have a parity with the Euro, and therefore are not appropriate for use. As a result, the most viable option found was to extrapolate the costs from those of building a hospital in Portugal.

The Hospital de Proximidade de Sintra is currently under construction, with its opening scheduled for the end of 2023 (Câmara Municipal de Sintra, 2021). The total planned investment is €75 million, of which €22 million correspond to the acquisition and installation of equipment (Agência Lusa, 2021). The remaining €53 million are assumed to correspond to the establishment cost. According to Câmara Municipal de Sintra (2021), the hospital will have a gross floor area of around 26,000 m^2. Based on this information, *Google Maps* was used to measure the area of the three existing blood centres in Portugal. The CSTP has an approximate area of 1,600 m^2, the CSTC 1,500 m^2 and the CSTL 1,100 m^2. Thus, their average area is 1,400 m^2. It is then assumed that this is the expected area for the blood centres to be established in the candidate locations. Through simple mathematical calculations, and taking the costs budgeted for the Hospital de Proximidade de Sintra as a reference, it is estimated that the establishment cost of a 1,400 m^2 facility is around €2.85 million. The cost of acquiring and installing the necessary equipment is around €1.2 million. It is clear that the equipment in a blood centre is different from that in a hospital, but given the lack of data, this was the extrapolation possible.

The above figures are assumed to correspond to the candidate blood centre's current capacity level – level 1 (q_{k_1}). For capacity level 2 (q_{k_2}), which represents a 25% increase in the capacity of blood centres, it is assumed that both the cost of establishment and equipment are also increased by 25%. Table 6 summarises the values considered for both capacity levels.

Table 6 - Establishment and equipment costs for blood centres

	Existing blood centre		Candidate blood centre	
	Capacity level		Capacity level	
	q_{k_1}	q_{k_2}	q_{k_1}	q_{k_2}
Establishment cost – f'_{kq_k} (€)	0	712,500	2.85 million	3.5625 million
Equipment cost – e'_{kq_k} (€)	0	300,000	1.2 million	1.5 million

For existing blood centres with capacity level 1, both costs under analysis are zero. The costs of capacity level 2 for existing blood centres represent a 25% capacity expansion. Note that the difference between the costs of capacity levels 1 and 2 for candidate blood centres correspond exactly to the capacity expansion costs for existing blood centres.

Establishment and equipping costs of fixed blood collection units

Regarding fixed blood collection units, no data on establishment and equipment costs was found. Hence, these costs are inferred from those considered above for blood centres. Fixed blood collection units are intended only for donation collection and therefore perform fewer processes than blood centres. Besides, their collection capacity is smaller than that of blood centres. It follows that fixed blood collection units have lower establishment and equipping costs. Thus, both establishment and equipment costs are assumed to be one fifth of those set out above for blood centres, as shown in Table 7.

Table 7 - Establishment and equipment costs for fixed blood collection units

	Existing fixed blood collection unit		Candidate fixed blood collection unit	
	Capacity level		Capacity level	
	q_{j_1}	q_{j_2}	q_{j_1}	q_{j_2}
Establishment cost – f_{jq_j} (€)	0	142,500	570,000	712,500
Equipment cost – e_{jq_j} (€)	0	60,000	240,000	300,000

Collection and production costs

According to Ordinance 234/2015 issued by the Portuguese Ministry of Health, the collection cost per unit of WB is €21.07 (Coelho et al., 2015). However, the document does not specify the collection cost incurred in apheresis procedures. Given the specificity of the equipment required, it is assumed to be three times higher than the above. As such, it follows that $oc_{WB} = €21.07$ and $oc_{PLT-Apheresis} = €63.21$. With regard to production costs, Ordinance 234/2015 states that $pc_{RBC,WB} = €104.20/unit$, $pc_{PLT,WB} = €193.70/unit$ and $pc_{PLT,PLT-Apheresis} = €374.20/unit$.

Inventory holding, substitution, wastage, shortage and transport costs

The unit holding cost of each blood product at blood centres and demand nodes is defined based on the work of Dillon et al. (2017). According to the authors, the holding cost is €1/unit/day. Given the shelf life of blood products – up to 42 days for RBCs and 5 days for PLTs, it was decided to set the inventory holding costs through random value generation, since not all blood product units remain stored for equal periods. As such, it was assumed that $ic_{RBC,k} \sim random(1,42) = ic'_{RBC,h} \sim random(1,42)$ and $ic_{PLT,k} \sim random(1,5) = ic'_{PLT,h} \sim random(1,5)$. In fact, this is an option that better captures the actual operation of the BSC.

Unit values of substitution cost, shortage and wastage are also obtained from the above work. However, it is assumed that these parameters take the same value whatever the blood product. Therefore, it follows that $sc_{bb'} = €1300$, $wst_p = €130/unit$ and $stg_p = €1300/unit$ (Dillon et al., 2017).

Finally, the unit transport costs are defined according to the work of Rupprecht & Nagarajan (2015), which concerns refrigerated biological transport. It follows that $tc_{jk} = tc'_{nk} = tc''_{kh} = €0.14/km$.

5.2.2. Capacity parameters

Capacity of mobile blood collection units

As different collection facilities exist, it is expected that they have different collection capacities. The capacity of mobile blood collection units, n, is estimated based on their mode of operation. According to the literature reviewed, these collection facilities operate only for a few hours a day, which is also valid in the Portuguese context. Thus, their collection capacity is very small and 50 units per day is assumed, which amounts to 9,000 donations in each period in each mobile blood collection unit.

Capacity of fixed blood collection units

With regard to fixed blood collection units, j, their capacity is logically higher than the preceding ones as fixed units operate for a longer time. Thus, it is assumed that their collection capacity is 150 donations per day, which amounts to 27,000 donations per semester for each fixed blood collection unit.

Capacity of blood centres

In blood centres many processes are possible and therefore different capacities exist. The physical and human resources available in blood centres are naturally greater than in the previous collection facilities. As such, it is assumed that the collection capacity of blood centres is higher – 300 donations per day, which amounts to 54,000 donations per semester per blood centre. The production capacity was estimated taking into account the total production of RBCs and PLTs in 2019, which was 297,693

and 44,092 units, respectively. Given that there are currently three blood centres in the Portuguese BSC, and that each year has about 250 working days, the daily production of RBCs and PLTs is estimated to be about 400 and 60 units, respectively, in each of the blood centres. Thus, and assuming that the blood centres did not operate at the limit of their daily production capacity, this is considered to be 500 units of RBCs and 75 units of PLTs. Accordingly, the production capacity in each six-month period is 90,000 units of RBCs and 13,500 units of PLTs. Note that for RBCs, the maximum production capacity of the blood centres equals the sum of the maximum collection capacities in all the facilities concerned. After processing, all blood products have to be stored. Since the products are not immediately dispatched after their production, it is normal that there is previous inventory. Therefore, the daily storage capacity of blood centres is considered to be 25% higher than the production capacity. It follows that the half-yearly storage capacity in each blood centre is 112,500 units of RBCs and 16,740 units of PLTs.

All the above figures relate to capacity level 1. For capacity level 2, a 25% increase in all capacities is considered. Table 8 summarises the maximum unit capacities of each level in each blood facility. It should be reiterated that the selection of capacity levels only applies to fixed blood collection units and blood centres. Mobile blood collection units have a single donation capacity of 9,000 donations per semester and are excluded from the table below.

Table 8 - Capacity ceilings for fixed blood collection units and blood centres at each capacity level

Blood facility			Capacity level			
			1		2	
			Daily	Half-yearly	Daily	Half-yearly
Fixed blood collection unit	Collection		150	27,000	187	33,660
Blood centre	Collection		300	54,000	375	67,500
	Production	RBC	500	90,000	625	112,500
		PLT	75	13,500	93	16,740
	Storage	RBC	625	112,500	781	140,580
		PLT	93	16,740	116	20,880

Capacity of demand nodes

Finally, to determine the storage capacity of the demand nodes, since there is no public data on the subject, the 68-95-99.73 statistical rule was used. According to this rule, 99.73% of the data fall between values corresponding to the mean minus three times the standard deviation and the mean plus three times the standard deviation. Thus, the maximum demand value for each blood product in each demand node is considered to be the mean increased by three times the standard deviation. As explained in Subsection 5.2.7., when describing the uncertain parameters extrapolation, the demand follows a Poisson distribution. Although the 68-95-99.73 statistical rule is intended for the Normal distribution, it can also be applied to the Poisson distribution. In the Poisson distribution, the standard deviation is given by the square root of λ, a parameter that represents the semester demand in each demand node. In conclusion, the storage capacity of a given demand node is equal to the estimated six-month demand for each blood product for that same demand node plus three times the square root of that estimate.

5.2.3. Distance parameters

The parameters representing the distance between donor groups and collection facilities (∂_{ij}, ${\partial'}_{in}$ and ${\partial''}_{ik}$), between collection facilities and blood centres (${\partial'''}_{jk}$ and ${\partial''''}_{nk}$), and between blood centres and demand nodes (${\partial'''''}_{hk}$) are obtained via *Microsoft Excel* by applying the great circle distance formula, presented in equation (39), as in Samani et al. (2019). The geographical coordinates of the various locations were obtained from *Google Maps* in degrees and then converted to radians.

$$Distance_{ij} = 6{,}371 \times arccos\left[sin(LAT_i) \times sin\left(LAT_j\right) + cos(LAT_i) \times cos\left(LAT_j\right) \times cos\left(LONG_j - LONG_i\right)\right] \quad (39)$$

For the mdc parameter, a value of 30 km was set, as this is considered to be the maximum distance donors are willing to travel to donate. The maximum distance between collection units and blood centres should consider the processing time limit. As such, 150 km is considered for the mdp parameter, an appropriate figure that allows donations to be shipped within six hours from the time of collection. Finally, a value of 300 km was set for the mdd parameter. Thus, the maximum distance between blood centres and demand nodes allows the order to be fulfilled the same day it is placed and within a few hours.

5.2.4. Production parameters

The percentage of blood collected by each method that is actually processed is computed as the ratio of rejected donations to total donations collected in the year 2019. Donations are rejected when there are low or excessive donation volumes, or when problems occur during the shipping process, among others. Thus, it follows that $\varphi_{WB} = 0.99$ and $\varphi_{PLT-Apheresis} = 0.98$ (Escoval et al., 2020). According to Özener et al. (2019), each WB donation yields one transfusable unit of RBCs. In the case of PLTs, it is estimated that five WB donations are required to produce one transfusable unit. If the collection method used is PLT-Apheresis, one transfusable unit is obtained per donation (Instituto Português de Oncologia do Porto Francisco Gentil, 2020). Thus, it follows that $\delta_{RBC,WB} = 1$, $\delta_{RBC,PLT-Apheresis} = 0$, $\delta_{PLT,WB} = 0.2$ and $\delta_{PLT,PLT-Apheresis} = 1$.

5.2.5. Substitutability parameters

The ABO/Rh blood compatibility matrix, $\Delta_{bb\prime}$, is as previously shown in Table 1. Not all substitutions between blood types are equally preferred. The ABO group substitution priority matrix – $\nabla_{bb\prime}$, shown in Table 9, expresses the degree of preference of possible substitutions through weights. Thus, the most preferred relationships are assigned a value of 1/8 and the least preferred are assigned a value of 7/8. These weights are intended to be multiplied by the shortage cost, thereby resulting in the cost of substitution between each pair of compatible blood types, as in Dillon et al. (2017).

Table 9 - ABO group substitution priority matrix based on Dillon et al. (2019)

Blood type available	Blood type in demand							
	AB+	AB–	A+	A–	B+	B–	O+	O–
AB+	0	–	–	–	–	–	–	–
AB–	1/8	0	–	–	–	–	–	–
A+	2/8	0	0	–	–	–	–	–
A–	3/8	1/8	1/8	0	–	–	–	–
B+	4/8	0	0	0	0	–	–	–
B–	5/8	2/8	0	0	1/8	0	–	–
O+	6/8	0	2/8	0	2/8	0	0	–
O–	7/8	3/8	3/8	1/8	3/8	1/8	1/8	0

5.2.6. Environmental parameters

The carbon emission rates required are based on figures for Euro 6 class III refrigerated vans presented in the work of Yang et al. (2021). According to the authors, a full-laden refrigerated van is estimated to emit between 255 g/km and 322 g/km of carbon dioxide. Accordingly, it is assumed that the environmental parameters ce_{jk}, ce'_{nk} and ce''_{kh} take random values within this range. The impact of carbon emissions is quantified by the carbon cost and included in the objective function. According to Ember Climate (2021), the carbon cost on 07 October 2021 was €60.37/tonne.

5.2.7. Uncertain parameters

Supply

In the case of the uncertain supply parameter, several extrapolations were needed for it to be estimated, due to a lack of data. According to the IPST Activity Report 2019, the distribution of donations collected in mainland Portugal is as shown in Table 10, with a total of 300,888 donations collected in all existing collection facilities (Escoval et al., 2020).

Table 10 - Regional distribution of 2019 donations

Region	Donations
Alentejo	12,311
Algarve	10,036
Centre (including CSTC)	66,004
Lisboa e Vale do Tejo (including CSTL)	79,748
North (including CSTP)	132,789

Based on this information, the location of the donor groups is matched with the regions to which they belong. Next, the population density of the municipalities where the donor groups are located is used to weigh the annual donations. Again, it is assumed that more densely populated areas have greater potential for supply. This results in an estimate of the number of annual donations per donor group, presented in Table 11. Given the six-month length of each period, the values previously obtained are then divided by two semesters.

Table 11 - Annual and quarterly estimates of donor group supply

Donor group	Estimated annual donations	Estimated half-yearly donations
Almada	16,505	8,252
Amadora	52,592	26,296
Braga	19,881	9,940
Coimbra	7,470	3,735
Entroncamento	8,814	4,407
Olhão	10,036	5,018
Peniche	6,084	3,042
Peso da Régua	3,332	1,666
Porto	104,275	52,137
São João da Madeira	49,038	24,519
Viana do Castelo	5,300	2,650
Viseu	3,410	1,705

It should be noted that, for example, the Algarve region is represented in only one donor group – Olhão. This is why the value presented in Table 11 equals that of Table 10 for the Algarve region. In the case of the North region, where most donations are collected, the municipality with the highest population density is Porto (PORDATA, 2021). Hence, this is the donor group with the highest estimated number of donations. Additionally, it is necessary to know for each donor group the estimated donations per blood type. To this end, the estimated half-yearly donations are multiplied by the relative frequency of the various blood types in the Portuguese population. According to Duran et al. (2007), this is as presented in Table 12.

Table 12 - Distribution of blood types in the Portuguese population. Source: Duran et al. (2007)

Blood type (b)	Relative frequency
AB+	2.87%
AB–	0.57%
A+	38.89%
A–	7.71%
B+	6.41%
B–	1.27%
O+	35.28%
O–	7.00%

Since the data used to estimate the supply refers only to 2019, it is difficult to understand what type of probability distribution the data follow. Therefore, the Normal distribution is adopted, with the mean value μ being the estimated value for half-yearly donations of each donor group and blood type. The standard deviation, σ, is assumed to be 5% of the mean. *Microsoft Excel* is used to generate values according to a Normal distribution of known mean and standard deviation. In case the values returned are negative, which is not possible given the nature of the problem, they are assumed to be zero.

Demand

As far as demand is concerned, data must also be extrapolated. According to the IPST Activity Report 2019, 293,892 units of RBCs and 40,252 of PLTs were transfused in that year (Escoval et al., 2020). The latter value is aggregated and represents PLT transfusions from apheresis and WB donations, with and without pathogenic reduction. However, although the regional distribution of RBC transfusions is known, presented in Table 13, the PLTs one is not. It is then assumed that the regional distribution of PLTs transfusions is equal to that of RBCs. Note that the sum of the values in the right-

hand column of Table 13 does not equal 100% because transfusions in island regions are not included. From these data, it is possible to estimate the number of RBC and PLT units transfused in each region, resulting in the values presented in Table 14.

Table 13 - Regional distribution of RBC transfusions in 2019. Source: Escoval et al. (2020)

Region	Transfusions
Alentejo	3.93%
Algarve	3.65%
Centre	19.38%
Lisboa e Vale do Tejo	38.60%
North	31.14%

Table 14 - Estimated RBC and PLT transfusions per region in 2019

Region	RBC	PLT
Alentejo	11,549	1,581
Algarve	10,727	1,469
Centre	56,956	7,800
Lisboa e Vale do Tejo	113,442	15,537
North	91,517	12,534

Considering the location of the demand nodes, a match is made between these and the region to which they belong. Next, the population density of the municipalities where the demand nodes are located is used as a weighting factor. This results in an estimative of the annual demand per demand node, as shown in Table 15. Furthermore, this estimate is divided by two semesters, resulting in the estimated half-yearly demand for each demand node.

Table 15 - Estimated annual and quarterly demand of demand nodes

Demand node	Estimated annual demand		Estimated half-yearly demand	
	RBC	PLT	RBC	PLT
Almada	26,755	3,664	13,377	1,832
Amadora	85,251	11,675	42,625	5,837
Braga	13,774	1,886	6,887	943
Coimbra	6,446	882	3,223	441
Peniche	5,250	719	2,625	359
Portimão	10,727	1,469	5,363	734
Porto	72,244	9,894	36,122	4,947
São João da Madeira	42,315	5,795	21,157	2,897
Torres Novas	1,435	196	717	98
Viana do Castelo	3,672	502	1,836	251
Vila Real	1,826	250	913	125
Viseu	2,943	403	1,471	201

The next step is to estimate the demand for each product and blood type, at each demand node. The procedure is similar to that described above for the supply parameter. Thus, the half-yearly demand estimate is multiplied by the relative frequency of each blood type in the Portuguese population, previously presented in Table 12. According to Duan & Liao (2014), the demand for blood products follows a Poisson distribution of parameter λ. Hence, this is the distribution adopted and λ is assumed to be the half-yearly estimate of demand at each demand node, for each product and blood type.

5.2.8. Other parameters

The probability of occurrence of each scenario, π_s, should take into account the expected future variation in both supply and demand. Regarding demand, the Portuguese population is quite aged, since 21% are over 65 years old, which may indicate a higher demand for health care in the future and, consequently, for blood products (Organisation for Economic Co-operation and Development, 2019). However, on the other hand, there is an international therapeutic trend towards a lower use of blood products (Escoval & Marques, 2020c). Therefore, the future demand pattern in Portugal is not clear. According to Rapaport (2019), "(...) the demand for blood transfusions will increase further", the author

quotes in reference to the main findings of a study conducted on the global need and availability of blood products. As such, a future increase in demand is assumed more likely, compared to 2019 data.

In the case of supply, there is a clear trend in the reduction of donations and the number of donors in Portugal, also accentuated by the ageing population (Escoval et al., 2020). In this sense, it is considered more likely that supply will decrease in the future, compared to the figures for 2019.

Given the previous qualitative analysis, the following probabilities were assumed:

$$P(Estimated\ 2019\ supply) = 0.3 \qquad P(Estimated\ 2019\ demand) = 0.3$$
$$P(-10\%\ of\ estimated\ 2019\ supply) = 0.5 \qquad P(-10\%\ of\ estimated\ 2019\ demand) = 0.2$$
$$P(+10\%\ of\ estimated\ 2019\ supply) = 0.2 \qquad P(+10\%\ of\ estimated\ 2019\ demand) = 0.5$$

Assuming that the future supply and demand evolution events are independent, the probabilities of each of the nine scenarios, presented below in Table 16, are derived. The most likely scenario, S6, combines a reduction in supply with an increase in demand and the least likely is exactly the opposite, S8, which combines an increase in supply with a reduction in demand.

Table 16 - Estimated probability of occurrence of each scenario

Scenario	Probability of occurrence
S1	9%
S2	6%
S3	15%
S4	15%
S5	10%
S6	25%
S7	6%
S8	4%
S9	10%

Finally, the parameter ω, which represents a very large number, was assigned the value of 1×10^9.

5.3. Chapter conclusions

This chapter explains the procedures adopted to define the sets, the research and data treatment to obtain the various parameters and the assumptions made. Regarding the constitution of the sets of locations, the main decision criterion was population density, assuming that more densely populated municipalities have greater supply potential. It was concluded that in mainland Portugal there are six districts in which none of the municipalities has a population density equal to or greater than the average. Thus, all analysis is limited to the remaining 12 districts. Due to computational limitations, the size of the sets must also be reduced so that the model produces results in acceptable timescales. Thus, not all entities of the Portuguese BSC are included. As regards parameters, preference was given to the search in related literature and in official IPST documents. However, this was not always possible. Due to a lack of data, several extrapolations and assumptions were made. Supply is assumed to follow a Normal distribution and demand a Poisson distribution.

Next, Chapter 6 presents the results of implementing both the deterministic and stochastic approaches of the model to the case of the Lisboa e Vale do Tejo region. Furthermore, a comparative and critical analysis of the results is performed. This is followed by the implementation of an instance covering a larger geographical area.

6. Results and discussion

This chapter presents and discusses the results obtained from the various computational experiments carried out. These experiments were run using the GAMS modelling system through the IBM ILOG CPLEX 35.2.0 solver in multi-thread mode on a computer with two 6-Core 3.33 GHz Intel® Xeon® X5680 processors with 12 threads and 24.0 GB of RAM. The generic model developed is first applied to a simpler example, the case of the Lisboa e Vale do Tejo region, using both deterministic and stochastic approaches, in order to ascertain its validity. These experiments are duly documented in Section 6.1., consisting of two subsections. Subsection 6.1.1. concerns the results of the deterministic approach and Subsection 6.1.2. concerns the results of the stochastic approach. Section 6.2 describes the various attempts made to implement the model to a larger dataset of the Portuguese BSC. Finally, Section 6.3. concludes the chapter.

6.1. Lisboa e Vale do Tejo case

Section 6.1. aims to prove the validity of the developed optimisation model by applying both deterministic and stochastic approaches to a simpler case of the Portuguese BSC. The case is a down-scaled instance of the Portuguese BSC that aims at testing the model and ascertaining whether the results produced are as expected. Thus, the instance focuses only on part of the Portuguese BSC – the Lisboa e Vale do Tejo region, where demand is estimated to be higher than supply, given the most recent data disclosed. As such, it is a region that, from the point of view of SC efficiency and sustainability, is worth studying.

It is expected that the runtime of both the deterministic and stochastic approaches is long, as the generic model is made up of 19 types of variables – eight of them binary and 11 positive integer. Of the latter, most have six indices. In addition, there are five sets of locations and the greater the number of locations per set, the more complex the model becomes. All these features contribute for the model execution to be a time-consuming process. In this sense, it was decided to include in this case only three elements in sets I, J, K, N and H.

The set of donor groups, I, includes the locations of Entroncamento, Amadora and Almada, in accordance with what is presented in Section 5.1. These municipalities are located in the districts of Santarém, Lisboa and Setúbal, respectively, which here are considered to constitute the Lisboa e Vale do Tejo region. Regarding fixed blood collection units, J, only three locations of currently existing units are considered – Hospital de S. José (Lisboa), Hospital de Torres Novas (Santarém) and Centro Hospitalar de Setúbal (Setúbal), which are included in Table C1 in Appendix C. The set of blood centres, K, includes one existing location – CSTL – and two candidates – the district capitals of Santarém and Setúbal. The selection of the locations of the mobile blood collection units, N, is also in accordance with what is presented in Section 5.1. These are Oeiras (Lisboa), Ferreira do Zêzere (Santarém) and Seixal (Setúbal). Finally, the selected demand nodes are those presented in Section 5.1. for the districts of Lisboa, Santarém and Setúbal. All parameters necessary for the implementation of the different model approaches take the values provided in Section 5.2. The time horizon was kept at two years, which implies that four planning periods are considered in each of the approaches. In the case of the stochastic

approach, not all nine defined scenarios are considered. Only the three scenarios with the highest probability of occurrence were selected – S3 (15%), S4 (15%) and S6 (25%).

Next, Subsection 6.1.1. presents and discusses the results obtained from applying the deterministic approach of the model and Subsection 6.1.2. presents the results obtained from applying the stochastic approach. Subsection 6.1.2. also includes the analysis of its results, which are compared with those obtained in the previous subsection.

6.1.1. Deterministic results

The deterministic approach of the optimisation model takes the supply and demand values estimated based on 2019 data, as set out in Subsection 5.2.7. The purpose of running the model according to this approach is to obtain an overview of the main performance indicators of the Portuguese BSC, although restricted to the Lisboa e Vale do Tejo region. That is, to know relevant quantities such as collection, production, wastage, substitution between blood types and shortage. In addition, it provides information on decisions regarding the establishment of blood facilities and allocations.

About an hour after the beginning of the run of this computational experiment, it was observed that the execution settled with a gap of 2.25% compared to the optimal solution. From then on, the progress was very slow and it was decided to stop the run after 16,933 seconds (about four hours and 40 minutes), with an approximate gap of 2.18%. Note that the deterministic approach of the model comprises in total 66 binary variables and 8,640 positive integer variables.

The solution obtained presents a total cost of €135,838,259.71 and the best possible solution of €132,877,450.06, the absolute gap being €2,960,809.65. The values of the various cost components are presented in Table 17. The components with the greatest share in the value of the objective function are the shortage cost, followed by the production and inventory holding costs. Contrarily, the cost of wastage is the second-least significant. In a first analysis, the quite expressive value of shortage was expected, since it is acknowledged that the Lisboa e Vale do Tejo region recurrently experiences a deficit in supply in face of demand.

Table 17 - Cost components of the deterministic approach of the Lisboa e Vale do Tejo case

	Absolute (€)	%
Establishment cost	0	-
Operating cost of collection	3,247,940.50	2.39
Transport cost	380,444.50	0.28
Inventory holding cost	6,168,051	4.54
Production cost	21,695,336.60	15.97
Substitutability cost	137,962.50	0.10
Shortage cost	104,140,400	76.66
Wastage cost	23,010	0.02
Environmental penalty	45,114.60	0.03

With regard to blood facility establishment and capacity selection decisions, the results show that the model does not establish any new blood centre. In the case of fixed blood collection units, the set considered did not include any candidate locations. Thus, the cost of establishment is non-existent. Capacity level 1 was selected for both the blood centre located in Lisboa (CSTL) and the three existing fixed units, indicating that the current capacity of the facilities is adequate and there is no need for

expansion. Table E1 in Appendix E presents the capacity utilisation rate, calculated as the ratio between used and available capacities. It can be seen that both the available collection and production capacity are not used close to 100%, which corroborates the model's decision to opt for level 1.

In terms of allocation decisions, all donor groups are allocated to at least one collection facility so that the full potential supply is available and can be collected. All fixed and mobile blood collection facilities are allocated to the existing blood centre in Lisboa, which is responsible for processing donations from these collection facilities. Finally, the three demand nodes covered are also allocated to the blood centre in Lisboa, the latter being responsible for dispatching all blood products in demand.

During the two-year time horizon, 150,050 donations were collected in the Lisboa e Vale do Tejo region, 14,300 of these in fixed blood collection units (9.5%) and the remainder in the blood centre (90.5%). This means that the existing mobile blood collection units did not collect any donations. In fact, the model favours collection in blood centres to avoid incurring transportation costs as donations from both fixed and mobile units must be shipped to the blood centre to which they are allocated for the collected donations to be processed. Thus, only donations collected in fixed blood collection units were actually shipped, which justifies the low relative contribution of transportation costs and environmental penalties to the objective function. Regarding the collection method, only 2,050 donations were obtained through PLT apheresis, which represents about 1.37% of total donations. This figure is in line with what actually happens in the Portuguese BSC, as only 2% of donations in 2019 originated from this method. The main factor behind the low representativeness of apheresis donations is its operational cost, since the equipment required is more expensive when compared to that required for WB collection. Furthermore, the quantities collected in each planning period are similar. In the fixed blood collection units, the lowest quantity collected was in period $t4$ with 3,201 donations and the highest was in period $t2$ with 3,932 donations. In the case of blood centres, the lowest quantity collected was in period $t3$ with 33,069 donations and the highest was in period $t4$ with 34,399 donations. Finally, it is important to compare the quantity collected with the available supply from the three donor groups. The Entroncamento donor group provided 14,300 donations, with an average potential supply of 17,628 donations; the Amadora donor group provided 103,706 donations, with an average potential supply of 105,184 donations; and the Almada donor group provided 32,044 donations, with an average potential supply of 33,010 donations. In summary, the Entroncamento, Amadora and Almada donor groups provided 81.1%, 98.6% and 97.1% of their estimated average potential. Note that the supply the model has available is randomly generated according to a Normal distribution of mean estimated based on known 2019 data and with standard deviation that is 5% of the mean. Thus, these donation rates in relation to potential supply are indicative values, as they were obtained by dividing the total donations from each donor group by the estimated supply for the two-year planning horizon.

After collection, donations are processed into transfusable units of RBCs and PLTs. Figure 9 presents the production obtained in the deterministic approach of the Lisboa e Vale do Tejo case. In total, 146,520 units of RBCs and 31,313 units of PLTs were produced during the planning horizon. Thus, it is verified that the blood product produced in larger quantities are RBCs, which was expected since the yield of WB collections is higher for this product. It is recalled that one unit of WB allows producing one unit of RBCs and only 0.2 units of PLTs. The quantity produced proves that the model behaves

exactly as assumed, since if the 2,050 donations of PLT apheresis are deducted from the 150,050 total donations, the result is that there were 148,000 donations of WB. Multiplying this value by the parameter $\varphi_{WB} = 0.99$, which represents the percentage of WB collected that is effectively processed, results in exactly 146,520 RBC units produced. In the case of PLTs, the 2,050 apheresis donations yield 2,009 transfusable units, since $\varphi_{PLT-Apheresis} = 0.98$. To these 2,009 units are added those that come from WB donations, i.e., $148{,}000 \times 0.2 \times 0.99 = 29{,}304$, thus making 31,313 transfusable units of PLTs. Regarding the blood types, there is a greater production of A+, O+, A– and O–. These are also the ones

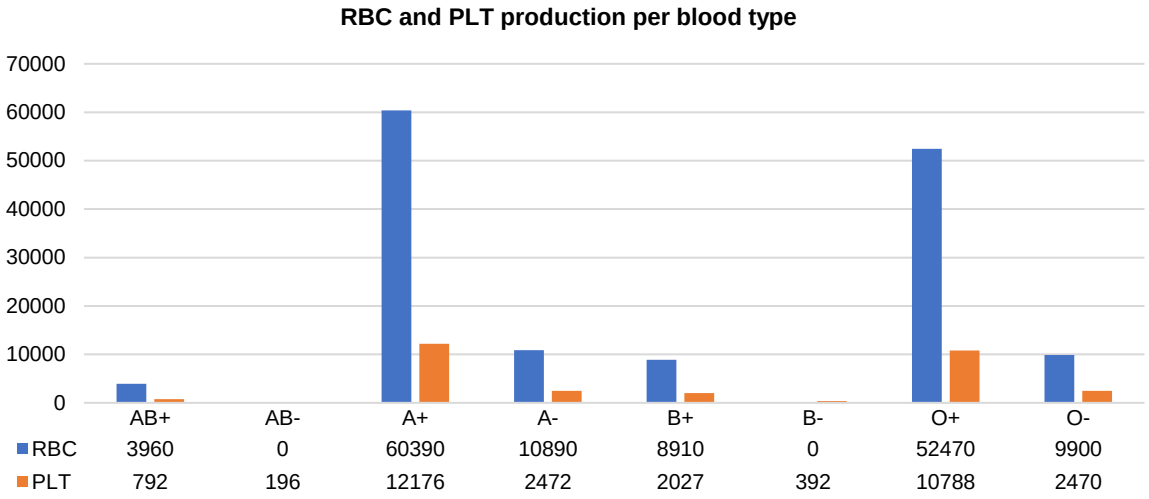

Figure 9 - Production resulting from the deterministic approach of the Lisboa e Vale do Tejo case

collected in greater quantity since they are the four most frequent in the Portuguese population.

All 146,520 units of RBCs produced are distributed and there is no wastage of this blood product. The same does not happen with PLTs. There are 31,136 units distributed, which means that 177 units are wasted in the blood centre. Even so, it should be noted that this is a negligible amount since it corresponds to only 0.56% of the total PLT production. The wastage of this product occurs in larger quantity for blood type A+, totalling 147 units. The reason for this wastage can easily be associated with the greater representativeness of this blood type in the Portuguese population. Since all the donations collected are necessarily processed in the widest possible range of blood products, it would be expected that, if there was PLT wastage, it would be more significant for the blood types that were collected in larger amounts. The remaining 30 units of wasted PLTs are of type O– (26 units), B+ (two units) and O+ (two units). Table E1 in Appendix E details the percentage wastage of each blood product and type, calculated as the ratio of the amount wasted to that produced.

Substitution between blood types occurs only for PLT units, which means that for RBCs all units of a given blood type are distributed to meet the demand for that same blood type. The quantities of PLTs substituted are presented in Table 18, totalling 607 units. This is a minor figure, as it represents only 1.95% of the total PLTs distributed over the two-year time horizon. This value can be found in Table E1 in Appendix E which presents the fraction of blood products that are distributed on a substitution basis. The three most substituted blood types are O+ (260 units), followed by A+ (132 units) and AB+ (121 units). In contrast, the least substituted blood type is B+ (10 units).

Table 18 - Total number of PLTs substituted in the deterministic approach of the Lisboa e Vale do Tejo case

Substituted blood type	Substitute blood type	PLT units
AB+	AB–	58
AB+	A+	44
AB+	B+	19
AB–	A–	3
AB–	B–	16
A+	A–	44
A+	O+	88
A–	O–	33
B+	B–	10
B–	O–	32
O+	O–	260

Since all RBC production is distributed, it turns out that there is a shortage of this blood product in quite significant quantities. In fact, the shortage cost is the largest portion of the total cost found for the deterministic approach of the Lisboa e Vale do Tejo case. The shortage of RBCs totals 80,099 units in two years. It is more frequent in the demand nodes of Lisboa and Santarém, being 74,040 units (92.44%) and 5,121 units (6.39%), respectively. The demand node of Setúbal faces the lowest shortage, of only 938 units (1.17%). Figure 10 depicts the relationship between the shortage quantities and the various blood types over the planning horizon. As might be expected, the most common blood types (A+, O+ and A–) are also those facing the greatest shortages in all periods. This is because despite being the most in supply, they are also the most in demand. The opposite reasoning is valid, since the less common blood types (AB+, B– and AB–) are also those that face the least shortage. Table E1 in Appendix E provides the service level for each blood product and type, which is calculated as the ratio of satisfied demand to observed demand.

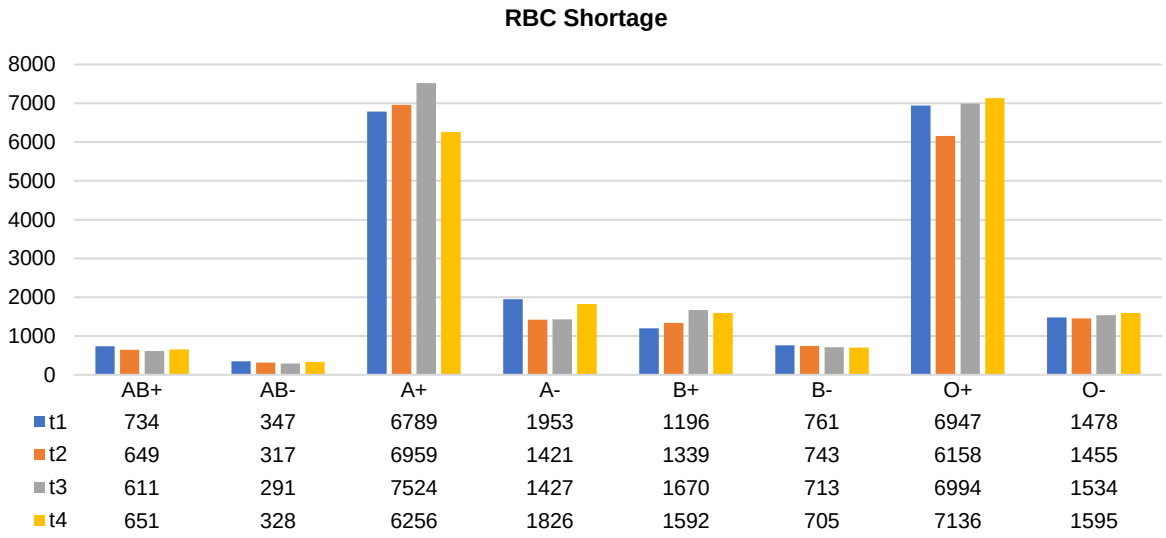

Figure 10 - Shortage resulting from the deterministic approach of the Lisboa e Vale do Tejo case

High shortages of RBCs are not surprising, as it is known that the Northern region of Portugal is where most donations are collected and that the region of Lisboa e Vale do Tejo is where the demand is greatest. The shortage observed could not be reduced by increasing, for example, the capacity of blood facilities, i.e., by selecting capacity level 2. The root of the problem lies in the potential supply from

donor groups, which is clearly insufficient to cover needs. Thus, it can be concluded that the results presented by the model are meaningful and in accordance with what was expected, thereby validating the mathematical formulation.

Next, Subsection 6.1.2 analyses the results of the stochastic approach of the model applied to the same case of the Lisboa e Vale do Tejo region.

6.1.2. Stochastic results

In the stochastic approach of the model developed, supply and demand are treated as uncertain parameters. The uncertainty inherent to them is handled by means of scenarios, each with a certain probability of occurrence. As mentioned in Section 6.1., only the three most probable scenarios are considered in the case studied. Of these, S3 combines the estimated 2019 supply with a 10% increase in estimated 2019 demand; S4 combines a 10% reduction from estimated 2019 supply with estimated 2019 demand; and S6 combines a 10% reduction in estimated 2019 supply with a 10% increase from estimated 2019 demand. The aim of the stochastic approach is then to analyse the behaviour of the model against possible variations in supply and demand over time, and to assess the consequent impact on the network configuration and BSC performance.

Once the run of this computational experiment started, it was observed that after about two hours and 50 minutes the execution stabilised, presenting a gap of 4.07%. The run kept going until it was interrupted after 29,513 seconds (eight hours and 10 minutes) with an approximate relative gap of 4.06%. Note that the stochastic approach of the model comprises in total 66 binary variables and 25,920 positive integer variables.

The solution found has a total cost of €95,649,920.39, with the best possible solution costing €91,761,337.08. The absolute gap is therefore €3,888,583.31. Thus, it appears that de value obtained for the solution of the stochastic approach is lower than that of the deterministic approach. Table 19 presents the values taken by the various cost components of the objective function in the stochastic approach under analysis. It is noted that all components take lower absolute values when compared to those previously shown in Table 17. However, the analysis of the relative share of each component in the total cost reveals that shortage takes on greater significance in the stochastic approach than in the deterministic one. Another highlight is wastage, the cost of which is almost zero.

Table 19 - Cost components of the stochastic approach of the Lisboa e Vale do Tejo case

	Absolute (€)	%	Comparison with the deterministic approach (Δ%)
Establishment cost	0	-	-
Operating cost of collection	1,723,367.97	1.80	↓ 0.59
Transportation cost	189,497.85	0.20	↓ 0.08
Inventory holding cost	2,883,581.85	3.01	↓ 1.53
Production cost	11,431,556.18	11.95	↓ 4.02
Substitutability cost	59,840.63	0.06	↓ 0.04
Shortage cost	79,339,130	82.95	↑ 6.29
Wastage cost	474.50	0.00	↓ 0.02
Environmental penalty	22,471.40	0.02	↓ 0.01

With regard to establishment decisions and capacity selection, the results are broadly similar to those of the previous deterministic approach. This means that the three existing fixed blood collection

units are kept at their current capacity level – level 1, as is the blood centre in Lisboa. Neither of the two candidate blood centres is established.

All donor groups are allocated to at least one collection facility, be it a fixed or mobile blood collection unit or a blood centre. In the particular case of the donor group located in Almada, it is simultaneously allocated to two fixed units, two mobile units, and the existing blood centre, which means that donors may donate in five different collection facilities. This is possible because the distance the donor group is from these collection facilities is less than the maximum distance they are willing to travel to donate – mdc parameter. As regards the remaining allocation decisions, since there is only one blood centre, all fixed and mobile units are allocated to it, as well as the three demand nodes considered.

In the existing fixed blood collection units, 14,612 donations are collected in scenario S3, 13,419 in scenario S4 and 14,209 in scenario S6. This amounts to a total of 42,240 donations over the two-year planning horizon. The distribution of donations by blood type is in line with the frequency in the Portuguese population. That is, most of the donations collected are type A+, O+, A– and O–. Only in scenario S4, more donations are collected from type B+ than O–, B+ being the fifth most common blood type in Portugal. Regarding the collection method, 799 donations were collected by PLT apheresis in scenario S3, 1,595 in scenario S4 and 200 in scenario S6. These figures represent 5.5%, 11.9% and 1.4% of the total donations in each scenario, respectively. The 11.9% figure is noteworthy as it is higher than the current 2% figure in the Portuguese BSC. Given that scenario S4 considers a 10% reduction in supply compared to the estimated value based on 2019 data, the greater representativeness of apheresis collections compared to WB collections may stem from their higher profitability in PLTs. In short, the model favours a more efficient collection method to counteract the reduction in available supply.

Similar to the deterministic approach, no donations were collected in mobile blood collection units in the stochastic approach. By implementing a larger instance with a wider geographical coverage, it is expected that these units collect WB, especially from nearby donor groups who do not have other collection facilities easily accessible.

In the blood centre currently operating in Lisboa, 136,038 donations were collected in scenario S3, 121,331 in scenario S4 and 121,941 in scenario S6, totalling 379,310 donations collected over the two-year planning horizon. It can be seen that the most commonly collected blood types follow the relative frequency distribution for the Portuguese population in all scenarios. WB collection was the most commonly used method and also the most cost-effective. 2,351 donations were collected by PLT apheresis in scenario S3, 3,155 in scenario S4, and 4,950 in scenario S6. These figures represent 1.7%, 2.6% and 4.1% of the total donations in each scenario, respectively.

The total donations resulting from the stochastic approach are as presented in Figure 11.

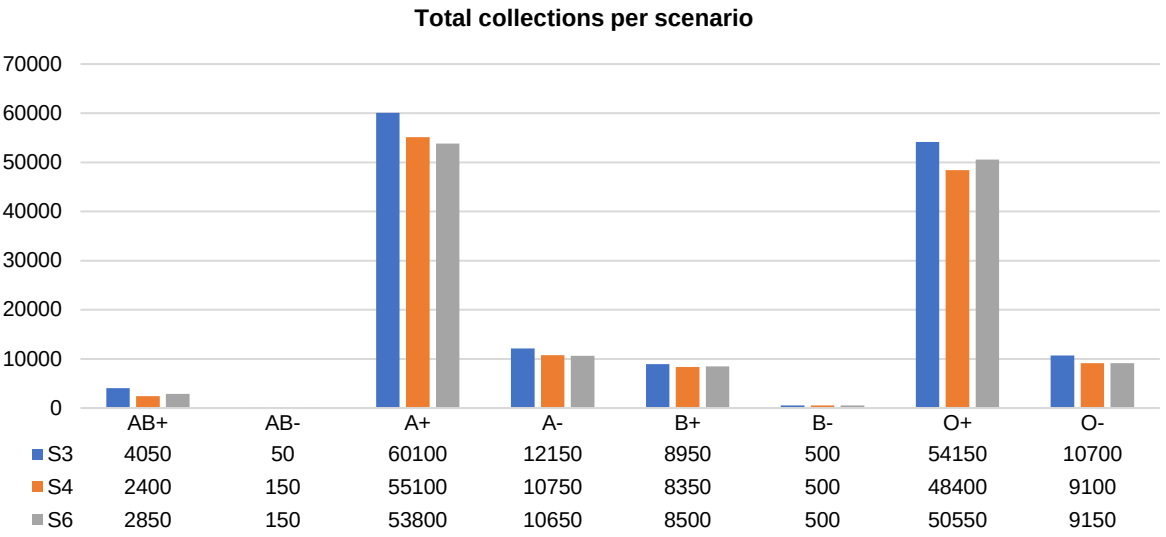

Figure 11 - Donations collected in the stochastic approach of the Lisboa e Vale do Tejo case

Furthermore, Table 20 distinguishes donations by collection method. The representativeness of PLT apheresis donations in scenario S3 is in line with what is currently observed. It is recalled that this scenario forecasts that supply remains in line with the 2019 estimate. Both scenarios S4 and S6 foresee a 10% reduction in the 2019 estimated supply and there is a coincident increase in the representativity of PLT apheresis collections in these scenarios.

Table 20 - Two-year donations per collection method and per scenario in the stochastic approach

	S3	S4	S6
WB	147,500	130,000	131,000
PLT-Apheresis	3,150	4,750	5,150
PLT-Apheresis/Total	2.1%	3.5%	3.8%

Finally, it is of interest to compare the donations collected with the available supply potential. Thus, for each donor group and scenario, Table 21 presents the donations actually collected compared to the potential for each donor group. Donations collected from donor groups located in Amadora and Almada are very close to the maximum available supply. In the case of the Entroncamento donor group, the realised supply potential is lower than the previous ones, but still quite significant and close to 90% for the most probable scenario, S6.

Table 21 - Potential supply realised in each scenario for each donor group

		Entroncamento	Amadora	Almada
Donations	S3	14,612	103,664	32,374
	S4	13,419	92,513	28,818
	S6	14,209	92,430	29,511
Potential supply	S3	17,628	105,184	33,010
	S4	15,865	94,665	29,709
	S6	15,865	94,665	29,709
Potential supply realised	S3	82.9%	98.6%	98.1%
	S4	84.6%	97.7%	97.0%
	S6	89.6%	97.6%	99.3%

After processing the donations collected, the production of RBCs resulted in 146,025 units in scenario S3, 128,700 units in scenario S4 and 129,690 units in scenario S6. PLT production is naturally

lower. This resulted in 32,292 units in Scenario S3, 30,395 units in Scenario S4 and 30,985 units in Scenario S6. Figures 12 and 13 present the production of RBCs and PLTs, respectively, by blood type. Overall, for all blood products and types, production in scenario S3 was higher than in scenarios S4 and S6, which was expected given the 10% reduction in supply for the latter.

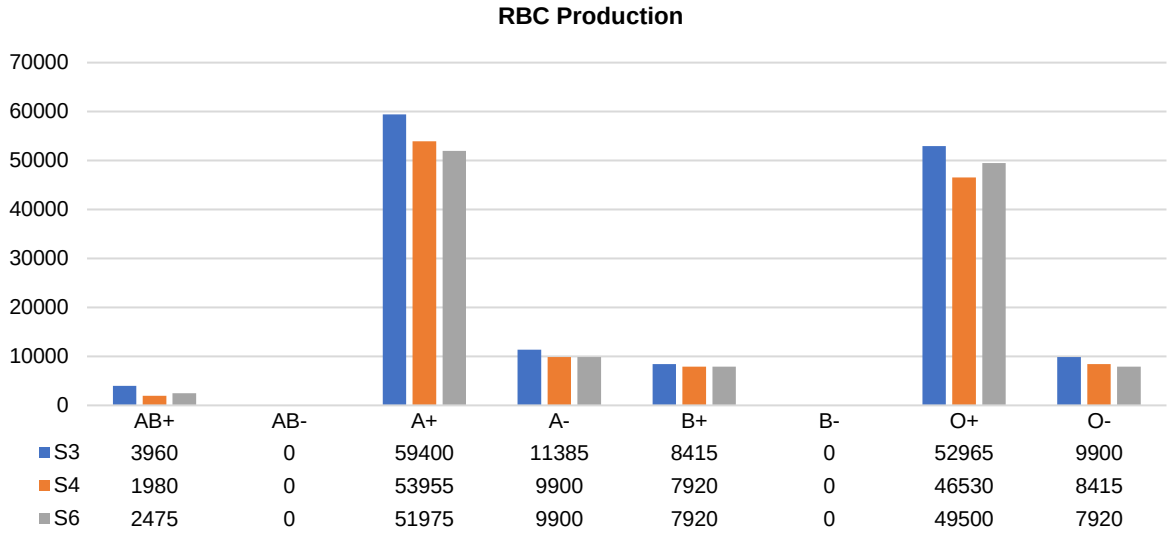

Figure 12 - RBC production resulting from the stochastic approach of the Lisboa e Vale do Tejo case

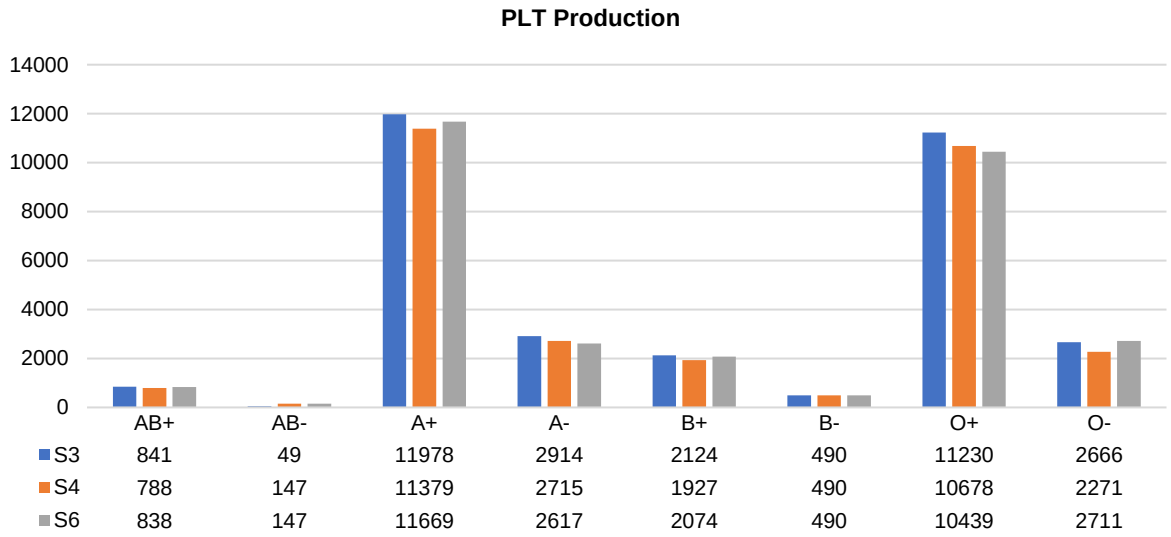

Figure 13 - PLT production resulting from the stochastic approach of the Lisboa e Vale do Tejo case

All RBC production is distributed, in all scenarios under analysis, meaning that there is no wastage of this blood product. In contrast, there is a shortage in large quantities. PLT production is almost fully distributed, with only 23 units being wasted in the existing blood centre. Of these, 20 units are wasted in scenario S3, one unit in scenario S4 and two units in scenario S6. The total wastage in the stochastic approach is then negligible, which corroborates the very low share that the wastage cost represents in the objective function. However, part of the distributed PLTs are on a substitution basis. Table 22 explains which blood types are substituted and which are substitutes. It is verified that the scenario in which there is the largest quantity substituted is S3, with 808 units, followed by S4, with 784 units, and S6, with 510 units. In scenarios S3 and S4, the most substituted blood type coincides with the most

common in Portugal – A+. In scenario S6 the most substituted blood type is the O+, which proceeds the A+ in the relative frequency distribution.

Table 22 - Total number of PLTs substituted in the stochastic approach

Substituted blood type	Substitute blood type	PLT units substituted		
		S3	S4	S6
AB+	AB–	-	37	43
AB+	B+	-	13	-
AB–	B–	51	37	38
A+	A–	388	408	120
A–	O–	-	151	30
B+	B–	22	83	28
B–	O–	3	19	-
O+	O–	344	36	251

Finally, it is worth analysing shortages. Figure 14 details the quantities in short supply at the demand nodes in each scenario. It can be seen that there is a shortage of RBCs of all blood types, although this is of more concern in the case of the most common ones, namely A+ and O+. The least shortage corresponds to the least frequent blood type, i.e., AB–. Shortages exist in all the scenarios analysed but are more significant in the S6 scenario where supply is reduced and demand increases compared to the 2019 estimates.

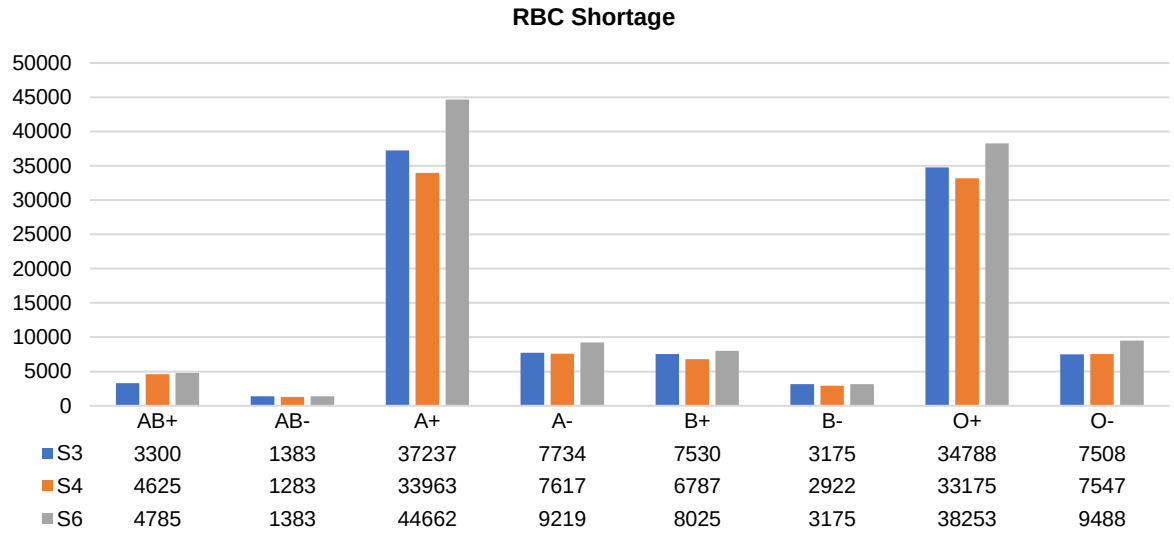

Figure 14 - Shortage of RBCs per blood type resulting from the stochastic approach of the Lisboa e Vale do Tejo case

Although there is PLT wastage, there is simultaneously a shortage of this blood product. However, the shortage of PLTs is considerably less than that of RBCs. Figure 15 details the blood types in short supply in each scenario. Again, it is in scenario S6 that the shortage is the highest and it occurs also for the most common blood types in Portugal. Only in scenario S4 and for blood type A- there is no unit of PLTs in short supply. The 20 units wasted in scenario S3 are type B+ and were discarded in period $t3$. Although 56 B+ units are found to be in short supply in the said scenario, the detailed analysis of the results show that this shortage occurs in the planning periods $t2$ and $t4$. As such, it would not be possible to avoid wastage while simultaneously filling the shortage.

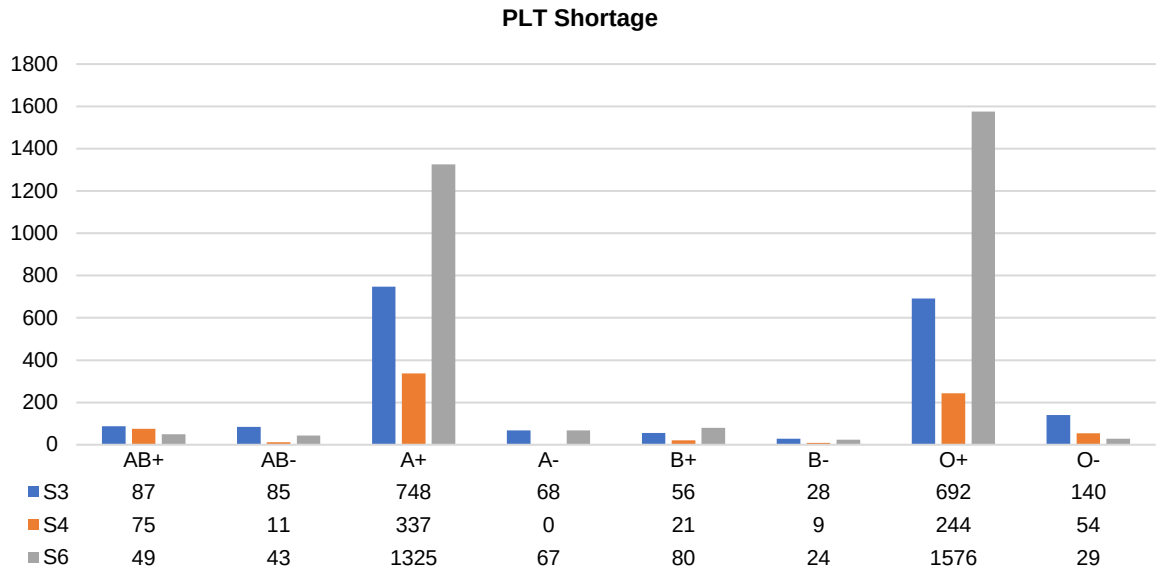

Figure 15 - Shortage of PLTs per blood type resulting from the stochastic approach of the Lisboa e Vale do Tejo case

Figures 16 and 17 present the distribution of the shortage quantities of RBCs and PLTs in each demand node and scenario. In general, the demand nodes with the highest shortage coincide with those with the highest demand – Amadora and Almada. The scenario with the highest shortage is, for all blood products and demand nodes, the S6. This is an expected conclusion since it is the scenario that combines the reduction in supply with the increase in demand. It should also be noted that in scenario S4 there is no shortage of PLTs in Amadora.

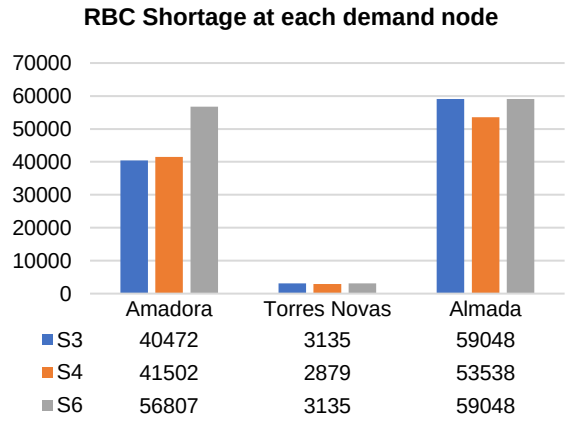

Figure 16 - Shortage of RBCs per demand node resulting from the stochastic approach of the Lisboa e Vale do Tejo case

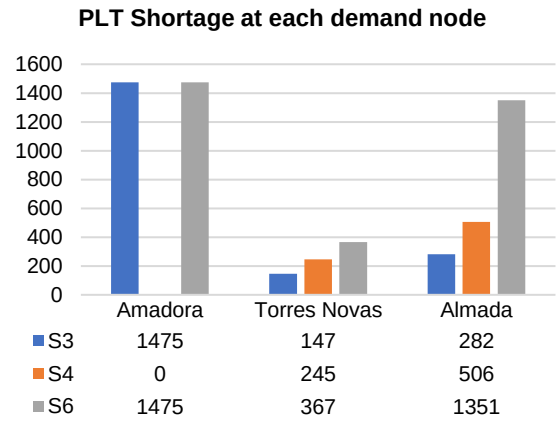

Figure 17 - Shortage of PLTs per demand node resulting from the stochastic approach of the Lisboa e Vale do Tejo case

For the stochastic approach, the blood facility establishment and capacity selection decisions, as well as the allocation decisions encountered, are similar to those of the previous deterministic approach. However, the analysis of the three most likely scenarios leads to the conclusion that the observed shortage tends to perpetuate and further increase, resulting in higher costs and lower service level. Nevertheless, as this case concerns only the Lisboa e Vale do Tejo region, the results should not be extrapolated to the whole country. Moreover, the real problem of the region analysed in this study would

not be solved with more collection facilities or with more available capacity of the existing facilities, since it lies in the specific supply of the region. The solution currently in force, to cover the existing shortage with surplus production from other regions of the country, particularly the North, seems to be the most appropriate, although it may entail high transport costs.

Next, Section 6.2 explains the procedures carried out in an attempt to implement the optimisation model developed for the Portuguese BSC case study.

6.2. IPST case study

The purpose outlined for this section was to present and analyse the results drawn from the implementation of the model in the context of the current Portuguese BSC, i.e., employing the sets and parameters duly described in Chapter 5. As such, Section 6.2. would be divided into two subsections, the first concerning the results of the deterministic approach and the second concerning the results of the stochastic approach. In this sense, a deterministic computational experiment was first run. The run stabilised after 20,750 seconds (about five hours and 45 minutes), presenting a gap of 45%. Thereafter the execution of this attempt proved to be extremely slow. The run was terminated after 126,575 seconds (about 35 hours and 10 minutes) due to an error in no way related to the mathematical formulation of the model or its implementation in GAMS – out of memory.

In view of this, it was decided not to proceed with the computational experiment of the stochastic approach that would also employ the sets and parameters presented in Chapter 5. This is because the inclusion of scenarios renders the execution even more complex and, consequently, more time consuming. Note that all 11 positive integer variables in the model depend on scenario s.

Still, a new attempt of computational experiment was made with a smaller deterministic instance. For each of the sets I, J, K, N, and H, only the locations within the districts of Aveiro, Coimbra, Leiria, Lisboa, Santarém and Setúbal were selected. The objective was to extend the implementation of the model to include the Centre coast region, together with the Lisboa e Vale do Tejo region. Thus, each of the sets of locations would consist of six elements. The run stabilised quickly, at just 1,697 seconds, with a gap of 48.50%. However, from then on it was extremely slow. After 105,582 seconds (29 hours and 20 minutes) there was still a gap of 48.10%. It was clear that the run would not be successful and it was decided to stop it. The resulting objective function value was €213,651,597.50 and the best possible solution would cost €110,890,411.42. Considering that the final gap is quite significant, the analysis of the results obtained would not be valid.

Nevertheless, it should be noted that the value of the best possible solution in this deterministic computational experiment that includes the Centre coast (Aveiro, Coimbra and Leiria) together with the Lisboa e Vale do Tejo region is lower than the best solution obtained in Subsection 6.1.1. for only the Lisboa e Vale do Tejo region (€110,890,411.42 versus €132,877,450.06). Given that the shortage cost represents in Subsection 6.1.1. the largest cost share of the objective function, it is assumed to be lower in this run, thus resulting in a lower total cost. In fact, if one considers the donor group located in São João da Madeira (Aveiro), for example, it appears that its potential six-month supply is very close to that of the donor group located in Amadora (Lisboa), i.e., 49,038 versus 52,592 donations, respectively. However, the difference between the estimated six-month demand for the demand nodes of these

districts is much more significant. In Aveiro 21,157 units of RBCs and 2,897 units of PLTs are demanded while in Lisboa 42,625 units of RBCs and 5,837 units of PLTs are demanded. The comparison between these data suggests that the supply collected in Aveiro is more than sufficient to meet the demand observed there and may also contribute to meet that of the Lisboa e Vale do Tejo region, thus reducing the existing shortage.

In order to better understand the trade-off between supply and shortage, another computational experiment was carried out. To the deterministic instance of the Lisboa e Vale do Tejo region was added the donor group located in Peniche (Leiria) and the mobile blood collection unit in Bombarral (Leiria). No extra demand nodes were added. The aim was therefore to increase the available supply to meet the demand from Lisboa e Vale do Tejo. The run stabilised 3,130 seconds (less than an hour) after its start, with a gap of 1.90%. However, after 30,576 seconds (about 8 hours and 30 minutes) it still had a gap of 1.84%. It was decided to stop the run and the solution obtained has a cost of €123,161,009.43. The best possible solution costs €120,890,058.33, and the absolute gap is €2,270,951.10. Table 23 presents the various cost components.

Table 23 - Cost components of the deterministic approach applied to the Lisboa e Vale do Tejo region together with Leiria

	Absolute (€)	%	Comparison with the deterministic approach (Δ%)
Establishment cost	0	-	-
Operating cost of collection	3,378,574.50	2.74	↑ 0.35
Transportation cost	437,735.00	0.36	↑ 0.08
Inventory holding cost	6,476,744.00	5.26	↑ 0.72
Production cost	22,665,207.60	18.40	↑ 2.43
Substitutability cost	78,000.00	0.06	↓ 0.04
Shortage cost	89,971,700.00	73.05	↓ 3.61
Wastage cost	101,140.00	0.08	↑ 0.06
Environmental penalty	51,908.34	0.04	↑ 0.01

In fact, shortage has decreased, as would be expected. In contrast, with the exception of substitutability, all other cost components increase. Even so, the solution obtained in this computational experiment is lower than the one obtained in the deterministic approach described in Subsection 6.1.1. by €12,677,250.28.

The donor group located in Peniche contributed with 11,545 WB donations collected in the mobile blood collection unit in Bombarral. The remaining donations are as explained in the previous Subsection 6.1.1. Overall, the shortage was reduced by 10,890 units of RBCs. However, only for six of the eight blood types. The biggest reduction is for type O+, with 3,465 fewer units in shortage. This is followed by type A+, with 2,970 units, type B-, with 1,980 units, type B+ and type A- with 990 units and finally type O-, with 495 fewer units in short supply. These results suggest that the model, when applied to more balanced instances both in terms of supply and demand, produces results in line with the actual operation of a BSC. Even so, as this is a very small deterministic instance, it is not possible to extrapolate results applicable to the whole Portuguese context.

6.3. Chapter conclusions

Following all these running attempts described above, it was concluded that, given the computational resources available, it would not be possible to obtain results that would allow a comprehensive analysis of the Portuguese BSC. However, despite the difficulties encountered in running the model with the various instances, the results of the Lisboa e Vale do Tejo region case prove that it is performing as expected. For the model to decide to establish candidate blood facilities it would be necessary for the available supply to be so high that existing facilities would not have the capacity to handle it. This is not the case in the Lisboa e Vale do Tejo region and, as such, the tactical-strategic decisions presented are unequivocally the most appropriate given the data input.

Thus, although the model has been validated, it would be interesting if it were subjected to an efficient solution strategy. For example, decomposition, in order to be able to be tested in more complex cases.

Next, Chapter 7 closes this study by presenting a summary of the main conclusions. In addition, the current state-of-the-art in SCND under uncertainty in the blood domain is discussed. Given the contribution of this work, thoughts on the most prominent topics for future research are presented.

7. Conclusions and future research

The BSC is essentially composed of collection and production facilities, and demand nodes. It is organised into four echelons – collection, production, inventory and distribution, which ensure the flow of blood products from donors to transfusion recipients. This is a SC which is particularly complex to manage as blood is perishable and there is not only a multiplicity of products with different shelf lives and storage conditions, but also of blood types. The importance of blood in any healthcare system is widely recognised, being used in cancer treatments, burns, surgeries such as transplants and others. As such, demand is irregular, as although there are scheduled treatments, trauma situations or urgent surgeries are uncertain. In addition, it is a human product which has no substitute and whose supply in developed countries depends on voluntary donation, which is also uncertain. Thus, it follows that when scarce, human lives can be put at risk.

Given the importance of its availability, for several decades research has been dedicated to understanding which are the best practices in inventory management. However, recent developments reveal an integrative trend, where all entities and processes in the BSC are considered. One of the themes recently addressed, albeit insufficiently, is the SCND. This falls within the scope of tactical-strategic planning and is responsible for the location and sizing of SC facilities, and therefore has long-term outcomes. Specifically, it has a profound impact on the efficiency of operations, cost structure and service level and is fundamental to support the strategy and objectives of the SC. In the case of blood, the network configuration should be designed with an orientation towards meeting demand, this being the most important factor. In addition to demand, wastage, shortages and operational costs should also be considered in the network design of the BSC. This is the focus of the present study.

Once the problem was contextualised, with emphasis on the particularities of the product, the existing literature on BSC management and SCND under uncertainty was reviewed. It was concluded that, although research on these topics has intensified, significant gaps still exist. Many existing network design optimisation models combine strategic decisions, such as the establishment of blood facilities, with operational decisions, taken in the short term. This is the case for problems including routing of mobile blood collection units or product shelf-life. At the tactical-strategic level, it does not make sense to plan for the shelf-life of products, which is only a few days, with the exception of plasma and cryo. In addition, some of the existing models do not address all echelons of the BSC, focusing only on some of them. Others consider uncertainty only in demand, or only in supply. Regarding the specific characteristics of the BSC, few models consider the various existing collection methods, the various products derived from WB or the substitutability between blood types. Today, social and environmental considerations are increasingly relevant and should be included in this problem. For all these reasons, there is a need to develop a generic optimisation model that contributes to the literature to date.

Therefore, a mixed integer linear programming model that resorts to two-stage stochastic programming is formulated to address both supply and demand uncertainty. It is a tactical-strategic model that can assist in decisions such as the establishment of blood facilities, the selection of their capacity levels and the allocation of donors to collection facilities, collection facilities to blood centres and demand nodes to blood centres. It is a comprehensive model that models the four echelons and

fills the gaps in the literature identified above. However, some assumptions are necessary. These are mostly related to relevant operational issues of the BSC. This is the case with the non-inclusion of the lateral transshipment process and inventory management. In particular, lateral transhipment is a daily practice in many countries and is key to balancing supply and demand between regions. That is, it simultaneously reduces wastage and shortages.

In order to apply the developed generic model to a real context, the Portuguese BSC, managed and regulated by IPST, is studied. Based on the analysis of IPST's activity data, it was found that there are significant inefficiencies in the wastage of some blood products and in the balance between demand and supply in certain regions. Considering that the inefficiencies identified severely hamper IPST's performance in the supply of blood products, there is a need to optimise the existing network configuration.

Consequently, the data required for the implementation of the model is researched and treated. Given the difficulties faced in data collection, some extrapolations are inevitable. This is the case for the estimation of establishment and equipment costs of both fixed blood collection units and blood centres. Both costs were extrapolated from the budgeted costs for the construction of a Portuguese hospital. Other cost parameters were obtained from related literature. However, because they refer to SCs in other countries, the costs considered may not be the most adjusted to the Portuguese context. In the case of the uncertain parameters, estimates are based on IPST public data from 2019. However, supply is assumed to follow a Normal distribution. This assumption does not allow, for example, to reproduce the seasonality that occurs for supply. On the other hand, according to the literature consulted, demand follows a Poisson distribution. There are also limitations to be pointed out regarding the calculated distances. The geographic coordinates of the various locations were obtained through *Google Maps* and the great circle distance formula was applied. However, in the real operation of the SC the vehicles do not move in a straight line, existing several routes. This means that the calculated distances tend to be shorter than the real distances to be covered.

Having said that, the model was implemented to the case of the Lisboa e Vale do Tejo region. Two computational experiments were performed – a deterministic and a stochastic approach, and the results were analysed. In both approaches it is notorious the great shortage that occurs. However, this was an expected result since the case study allowed assessing the imbalance between supply and demand in this region. Obviously, the shortage compromises the service level, which for some blood types of RBCs is just over 50%. These are worrying data, but which the model alone could not overcome, as supply is clearly limiting. All the tactical-strategic decisions presented are as expected, so the Lisboa e Vale do Tejo case allows the model to be validated. Nevertheless, an attempt was made to implement the model at a larger instance, covering 12 of the 18 districts of mainland Portugal. However, this computational experiment was not successful due to computational power limitations. In view of this situation, the size of the instance was reduced, covering only six districts. Even so, it was not possible to obtain reliable results within a reasonable time span.

In view of the above, it is suggested to implement the model to larger instances on computers with greater processing power so that the problem can be modelled comprehensively. If this is not possible, metaheuristics are an option to be considered. Although these solution approaches do not allow obtaining an optimal solution, they have a very significant contribution in reducing the time taken to obtain results. Therefore, a combination of exact methods, such as mixed integer linear programming, and metaheuristics is suggested – the so-called math-heuristics approach.

The model could also be used to study a disruptive case study, in order to evaluate the BSC in extreme situations.

Despite all the limitations of the computational experiments carried out, the generic model developed has proved to be valid and constitutes a contribution to the existing literature, which should be the subject of further research studies.

Bibliography

Abdulwahab, U., & Wahab, M. I. M. (2014). Approximate dynamic programming modeling for a typical blood platelet bank. *Computers and Industrial Engineering*, *78*, 259–270. https://doi.org/10.1016/j.cie.2014.07.017

Agência Lusa. (2021, April 16). Investimento de 250 milhões em novos hospitais e 68 milhões de euros em obras até final de 2022. Retrieved October 18, 2021, from https://observador.pt/2021/04/16/investimento-de-250-milhoes-em-novos-hospitais-e-68-milhoes-de-euros-em-obras-ate-final-de-2022/

Albareda-Sambola, M., Alonso-Ayuso, A., Escudero, L. F., Fernández, E., & Pizarro, C. (2013). Fix-and-Relax-Coordination for a multi-period location-allocation problem under uncertainty. *Computers and Operations Research*, *40*(12), 2878–2892. https://doi.org/10.1016/j.cor.2013.07.004

Alfonso, E., Xie, X., Augusto, V., & Garraud, O. (2012). Modeling and simulation of blood collection systems. *Health Care Management Science*, *15*(1), 63–78. https://doi.org/10.1007/s10729-011-9181-8

American Red Cross. (2021a). Facts About Blood and Blood Types. Retrieved March 1, 2021, from https://www.redcrossblood.org/donate-blood/blood-types.html

American Red Cross. (2021b). Plasma, Platelets and Whole Blood. Retrieved March 3, 2021, from https://www.redcrossblood.org/donate-blood/how-to-donate/types-of-blood-donations/blood-components.html

Arani, M., Chan, Y., Liu, X., & Momenitabar, M. (2021). A lateral resupply blood supply chain network design under uncertainties. *Applied Mathematical Modelling*, *93*, 165–187. https://doi.org/10.1016/j.apm.2020.12.010

Araújo, A. M., Santos, D., Marques, I., & Barbosa-Povoa, A. (2020). *Blood supply chain: a two-stage approach for tactical and operational planning*. *OR Spectrum* (Vol. 42). Springer Berlin Heidelberg. https://doi.org/10.1007/s00291-020-00600-1

Australian Red Cross. (2020). Blood component storage temperature range. Retrieved March 3, 2021, from https://transfusion.com.au/blood_products/storage/storage_temperature_range

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

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

Bish, D. R., Bish, E. K., Xie, S. R., & Slonim, A. D. (2011). Optimal selection of screening assays for infectious agents in donated blood. *IIE Transactions on Healthcare Systems Engineering*, *1*(2), 67–90. https://doi.org/10.1080/19488300.2011.609520

Blake, J. T., Hardy, M., Delage, G., & Myhal, G. (2013). Déjà-vu all over again: Using simulation to evaluate the impact of shorter shelf life for red blood cells at Héma-Québec. *Transfusion*, *53*(7), 1544–1558. https://doi.org/10.1111/j.1537-2995.2012.03947.x

Bruno, G., Diglio, A., Piccolo, C., & Cannavacciuolo, L. (2019). Territorial reorganization of regional blood management systems: Evidences from an Italian case study. *Omega (United Kingdom)*, *89*, 54–70. https://doi.org/10.1016/j.omega.2018.09.006

Câmara Municipal de Sintra. (2021). Novo Hospital de Sintra. Retrieved October 18, 2021, from https://novohospitaldesintra.pt/pt/

Carden, R., & DelliFraine, J. L. (2005). An examination of blood center structure and hospital customer satisfaction: What can centralized and decentralized blood centers learn from each other? *Health Marketing Quarterly*, *22*(3), 21–42. https://doi.org/10.1300/J026v22n03_03

Chaiwuttisak, P., Smith, H., Wu, Y., Potts, C., Sakuldamrongpanich, T., & Pathomsiri, S. (2016). Location of low-cost blood collection and distribution centres in Thailand. *Operations Research for Health Care*, *9*, 7–15. https://doi.org/10.1016/j.orhc.2016.02.001

Coelho, P. P., Morgado, C., Albuquerque, D. De, & Rodrigues, M. (2015). Portaria 234/2015. Retrieved October 16, 2021, from https://dre.pt/pesquisa/-/search/69968713/details/maximized

Cortinhal, M. J., Lopes, M. J., & Melo, M. T. (2019). A multi-stage supply chain network design problem with in-house production and partial product outsourcing. *Applied Mathematical Modelling*, *70*, 572–594. https://doi.org/10.1016/j.apm.2019.01.046

Dehghani, M., & Abbasi, B. (2018). An age-based lateral-transshipment policy for perishable items. *International Journal of Production Economics*, *198*(January 2017), 93–103. https://doi.org/10.1016/j.ijpe.2018.01.028

Dehghani, M., Abbasi, B., & Oliveira, F. (2021). Proactive transshipment in the blood supply chain: A stochastic programming approach. *Omega (United Kingdom)*, *98*, 102112. https://doi.org/10.1016/j.omega.2019.102112

Diário da República Eletrónico. (2021). Decreto-Lei n.º 41498. Retrieved February 24, 2021, from https://dre.pt/web/guest/pesquisa/-/search/521842/details/maximized?filterEnd=1958-12-31&sort=whenSearchable&filterStart=1958-01-01&q=1958&sortOrder=ASC&jp=true&fqs=1958&perPage=25

Dillon, M., Oliveira, F., & Abbasi, B. (2017). A two-stage stochastic programming model for inventory management in the blood supply chain. *International Journal of Production Economics*, *187*(May 2016), 27–41. https://doi.org/10.1016/j.ijpe.2017.02.006

Doerner, K. F., Gronalt, M., Hartl, R. F., Kiechle, G., & Reimann, M. (2008). Exact and heuristic algorithms for the vehicle routing problem with multiple interdependent time windows. *Computers and Operations Research*, *35*(9), 3034–3048. https://doi.org/10.1016/j.cor.2007.02.012

DOMAINE. (2010). Manual de Gestão de Dadores. Retrieved November 15, 2020, from http://www.ipst.pt/files/IPST/INFORMACAO_DOCUMENTACAO/manual_gestao_dadores.pdf

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

Duran, J. A., Chabert, T., Rodrigues, F., & Pestana, D. (2007). Distribuição Dos Grupos Sanguíneos Na População Portuguesa. *ABO - Revista de Medicina Transfusional*, *29*, 5–17.

Ember Climate. (2021). Daily Carbon Prices. Retrieved October 7, 2021, from https://ember-climate.org/data/carbon-price-viewer/

Ensafian, H., & Yaghoubi, S. (2017). Robust optimization model for integrated procurement, production and distribution in platelet supply chain. *Transportation Research Part E: Logistics and Transportation Review*, *103*, 32–55. https://doi.org/10.1016/j.tre.2017.04.005

Escoval, M. A., & Marques, V. (2020a). Plano de Atividades 2020. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Escoval, M. A., & Marques, V. (2020b). Plano Estatégico 2020 - 2022. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/planos-estrategicos

Escoval, M. A., & Marques, V. (2020c). Relatório de Gestão 2019. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/relatorios-de-gestao

Escoval, M. A., Condeço, J., Sousa, A. P., Ramoa, A., Lobo, I., Miranda, I., et al. (2018). Relatório de Atividade Transfusional e Sistema Português de Hemovigilância 2017. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Escoval, M. A., Condeço, J., Sousa, A. P., Ramoa, A., Caeiro, C., Lobo, I., et al. (2019). Relatório de Atividade Transfusional e Sistema Português de Hemovigilância 2018. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Escoval, M. A., Condeço, J., Sousa, A. P., Ramoa, A., Caeiro, C., Lobo, I., et al. (2020). Relatório de Atividade Transfusional e Sistema Português de Hemovigilância 2019. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Eskandari-Khanghahi, M., Tavakkoli-Moghaddam, R., Taleizadeh, A. A., & Amin, S. H. (2018). Designing and optimizing a sustainable supply chain network for a blood platelet bank under uncertainty. *Engineering Applications of Artificial Intelligence*, *71*(November 2017), 236–250. https://doi.org/10.1016/j.engappai.2018.03.004

Eskandarpour, M., Dejax, P., Miemczyk, J., & Péton, O. (2015). Sustainable supply chain network design: An optimization-oriented review. *Omega (United Kingdom)*, *54*, 11–32. https://doi.org/10.1016/j.omega.2015.01.006

Etablissement Français du Sang. (2021). Le sang et ses composants. Retrieved March 1, 2021, from https://en.efs.sante.fr/comprendre-quest-ce-que-le-sang/le-sang-et-ses-composants

European Blood Alliance. (2021). Portugal. Retrieved February 24, 2021, from https://europeanbloodalliance.eu/country/portugal/

European Commission. (2016). Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the implementation of directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC setting standards for qua. Retrieved September 10, 2021, from https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2016_129_en.pdf

Fahimnia, B., Jabbarzadeh, A., Ghavamifar, A., & Bell, M. (2017). Supply chain design for efficient and effective blood supply in disasters. *International Journal of Production Economics*, *183*, 700–709. https://doi.org/10.1016/j.ijpe.2015.11.007

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

Fattahi, M., Govindan, K., & Keyvanshokooh, E. (2017). Responsive and resilient supply chain network design under operational and disruption risks with delivery lead-time sensitive customers. *Transportation Research Part E: Logistics and Transportation Review*, *101*, 176–200. https://doi.org/10.1016/j.tre.2017.02.004

Fattahi, M., Govindan, K., & Maihami, R. (2020). Stochastic optimization of disruption-driven supply chain network design with a new resilience metric. *International Journal of Production Economics*, *230*(April), 107755. https://doi.org/10.1016/j.ijpe.2020.107755

Fragoulakis, V., Stamoulis, K., Grouzi, E., & Maniadakis, N. (2014). The cost of blood collection in Greece: An economic analysis. *Clinical Therapeutics*, *36*(7), 1028–1036. https://doi.org/10.1016/j.clinthera.2014.05.003

Govindan, K., Fattahi, M., & Keyvanshokooh, E. (2017). Supply chain network design under uncertainty: A comprehensive review and future research directions. *European Journal of Operational Research*, *263*(1), 108–141. https://doi.org/10.1016/j.ejor.2017.04.009

Gunpinar, S., & Centeno, G. (2016). An integer programming approach to the bloodmobile routing problem. *Transportation Research Part E: Logistics and Transportation Review*, *86*, 94–115. https://doi.org/10.1016/j.tre.2015.12.005

Habibi-Kouchaksaraei, M., Paydar, M. M., & Asadi-Gangraj, E. (2018). Designing a bi-objective multi-echelon robust blood supply chain in a disaster. *Applied Mathematical Modelling*, *55*, 583–599. https://doi.org/10.1016/j.apm.2017.11.004

Haghjoo, N., Tavakkoli-Moghaddam, R., Shahmoradi-Moghadam, H., & Rahimi, Y. (2020). Reliable blood supply chain network design with facility disruption: A real-world application. *Engineering Applications of Artificial Intelligence*, *90*(April 2019), 103493. https://doi.org/10.1016/j.engappai.2020.103493

Hamdan, B., & Diabat, A. (2020). Robust design of blood supply chains under risk of disruptions using Lagrangian relaxation. *Transportation Research Part E: Logistics and Transportation Review*, *134*(January 2018), 101764. https://doi.org/10.1016/j.tre.2019.08.005

Heidari-Fathian, H., & Pasandideh, S. H. R. (2018). Green-blood supply chain network design: Robust optimization, bounded objective function & Lagrangian relaxation. *Computers and Industrial Engineering*, *122*(July 2017), 95–105. https://doi.org/10.1016/j.cie.2018.05.051

Hemmelmayr, V., Doerner, K. F., Hartl, R. F., & Savelsbergh, M. W. P. (2010). Vendor managed inventory for environments with stochastic product usage. *European Journal of Operational Research*, *202*(3), 686–695. https://doi.org/10.1016/j.ejor.2009.06.003

Instituto Português de Oncologia de Lisboa Francisco Gentil. (2020). Seja dador de sangue. Retrieved October 27, 2020, from https://www.ipolisboa.min-saude.pt/porque-ajudar-o-ipo/seja-dador-de-sangue/

Instituto Português de Oncologia do Porto Francisco Gentil. (2020). Dádiva de Multicomponentes -

Serviço de Imuno-Hemoterapia. Retrieved October 9, 2020, from https://www.ipoporto.pt/dev/wp-content/uploads/2014/01/Multicomponentes_FINAL.pdf

IPST. (2020). História. Retrieved February 24, 2021, from http://www.ipst.pt/index.php/pt/institucional/historia

IPST. (2021). Como organizar uma sessão de colheita. Retrieved February 25, 2021, from http://www.ipst.pt/index.php/pt/como-organizar-uma-sessao-de-colheita

Jabbarzadeh, A., Fahimnia, B., & Seuring, S. (2014). Dynamic supply chain network design for the supply of blood in disasters: A robust model with real world application. *Transportation Research Part E: Logistics and Transportation Review*, *70*(1), 225–244. https://doi.org/10.1016/j.tre.2014.06.003

Jafarian, E., Razmi, J., & Baki, M. F. (2018). A flexible programming approach based on intuitionistic fuzzy optimization and geometric programming for solving multi-objective nonlinear programming problems. *Expert Systems with Applications*, *93*, 245–256. https://doi.org/10.1016/j.eswa.2017.10.030

Katsaliaki, K., Mustafee, N., & Kumar, S. (2014). A game-based approach towards facilitating decision making for perishable products: An example of blood supply chain. *Expert Systems with Applications*, *41*(9), 4043–4059. https://doi.org/10.1016/j.eswa.2013.12.038

Lee, Y. H., Jung, J. W., & Jeon, Y. S. (2007). An effective lateral transshipment policy to improve service level in the supply chain. *International Journal of Production Economics*, *106*(1), 115–126. https://doi.org/10.1016/j.ijpe.2006.05.007

Leitão, M. do C. (2020). *COVID-19: impacto nos serviços de sangue e de medicina transfusional*. https://doi.org/10.25758/set.2265

Lowalekar, H., & Ravichandran, N. (2010). Model for blood collections management. *Transfusion*, *50*(12 PT2), 2778–2784. https://doi.org/10.1111/j.1537-2995.2010.02944.x

Lowalekar, H., & Ravichandran, N. (2011). A model for blood components processing. *Transfusion*, *51*(7 PART 2), 1624–1634. https://doi.org/10.1111/j.1537-2995.2011.03224.x

Mobasher, A., Ekici, A., & Özener, O. Ö. (2015). Coordinating collection and appointment scheduling operations at the blood donation sites. *Computers and Industrial Engineering*, *87*, 260–266. https://doi.org/10.1016/j.cie.2015.05.020

Moreno-Camacho, C. A., Montoya-Torres, J. R., Jaegler, A., & Gondran, N. (2019). Sustainability metrics for real case applications of the supply chain network design problem: A systematic literature review. *Journal of Cleaner Production*, *231*, 600–618. https://doi.org/10.1016/j.jclepro.2019.05.278

Muriel, A., & Simchi-Levi, D. (2003). Supply Chain Design and Planning – Applications of Optimization Techniques for Strategic and Tactical Models. In *Handbooks in Operations Research and Management Science* (pp. 15–93). https://doi.org/10.1007/978-3-642-20381-7_2

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

National Blood Transfusion Service, G. of M. (2020). History of blood. Retrieved March 2, 2021, from https://deputyprimeminister.gov.mt/en/nbts/Pages/About-Blood/History-of-Blood.aspx

Optimal Blood Use Project. (2010). Manual para Uso Óptimo do Sangue. Retrieved March 6, 2021, from http://ipst.pt/files/IPST/INFORMACAO_DOCUMENTACAO/manual_para_uso_optimo_do_sangue.pdf

Organisation for Economic Co-operation and Development. (2019). Portugal: Perfil de Saúde do País 2019. https://doi.org/10.1787/75b2eac0-pt

Organização Mundial da Saúde. (2010). Rastreio de dádivas de sangue para detecção de infecções transmissíveis por transfusão: recomendações. Retrieved December 3, 2020, from https://apps.who.int/iris/bitstream/handle/10665/44202/9789248547881_por.pdf?sequence=9&isAllowed=y

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

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

Osorio, A. F., Brailsford, S. C., Smith, H. K., & Blake, J. (2018). Designing the blood supply chain: how much, how and where? *Vox Sanguinis*, *113*(8), 760–769. https://doi.org/10.1111/vox.12706

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

Özener, O. Ö., & Ekici, A. (2018). Managing platelet supply through improved routing of blood collection vehicles. *Computers and Operations Research*, *98*, 113–126. https://doi.org/10.1016/j.cor.2018.05.011

Özener, O. Ö., Ekici, A., & Çoban, E. (2019). Improving blood products supply through donation tailoring. *Computers and Operations Research*, *102*, 10–21. https://doi.org/10.1016/j.cor.2018.09.003

Paterson, C., Kiesmüller, G., Teunter, R., & Glazebrook, K. (2011). Inventory models with lateral transshipments: A review. *European Journal of Operational Research*, *210*(2), 125–136. https://doi.org/10.1016/j.ejor.2010.05.048

Pereira, A. (2005). Blood inventory management in the type and screen era. *Vox Sanguinis*, *89*(4), 245–250. https://doi.org/10.1111/j.1423-0410.2005.00700.x

Perera, G., Hyam, C., Taylor, C., & Chapman, J. F. (2009). Hospital Blood Inventory Practice: The factors affecting stock level and wastage. *Transfusion Medicine*, *19*(2), 99–104. https://doi.org/10.1111/j.1365-3148.2009.00914.x

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

PORDATA. (2021). Densidade Populacional. Retrieved October 9, 2021, from

https://www.pordata.pt/Municipios/Densidade+populacional-452

Puchinger, J., & Raidl, G. R. (2016). Combining metaheuristics and exact algorithms in combinatorial optimization: A survey and classification. In *Lecture Notes in Computer Science* (Vol. 3562, pp. 41–53). https://doi.org/10.1007/11499305_5

Rajendran, S., & Ravindran, A. R. (2017). Platelet ordering policies at hospitals using stochastic integer programming model and heuristic approaches to reduce wastage. *Computers and Industrial Engineering*, *110*, 151–164. https://doi.org/10.1016/j.cie.2017.05.021

Ramezanian, R., & Behboodi, Z. (2017). Blood supply chain network design under uncertainties in supply and demand considering social aspects. *Transportation Research Part E: Logistics and Transportation Review*, *104*, 69–82. https://doi.org/10.1016/j.tre.2017.06.004

Rapaport, L. (2019). Blood supplies inadequate in many countries. Retrieved October 14, 2021, from https://www.reuters.com/article/us-health-blood-supply-idUSKBN1XI2FL

Rupprecht, C., & Nagarajan, T. (2015). *Current Laboratory Techniques in Rabies Diagnosis, Research and Prevention*. https://doi.org/https://doi.org/10.1016/C2014-0-01041-6

Şahinyazan, F. G., Kara, B. Y., & Taner, M. R. (2015). Selective vehicle routing for a mobile blood donation system. *European Journal of Operational Research*, *245*(1), 22–34. https://doi.org/10.1016/j.ejor.2015.03.007

Samani, M. R. G., Hosseini-Motlagh, S. M., & Ghannadpour, S. F. (2019). A multilateral perspective towards blood network design in an uncertain environment: Methodology and implementation. *Computers and Industrial Engineering*, *130*(January), 450–471. https://doi.org/10.1016/j.cie.2019.02.049

SNS24. (2020). Posso dar sangue? Retrieved October 20, 2020, from https://www.sns24.gov.pt/guia/posso-dar-sangue/

Sousa, G. de, Miranda, I., Pires, I., Condeço, J., Escoval, M. A., Chin, M., & Santos, M. (2017). Relatório de Atividade Transfusional e Sistema Português de Hemovigilância 2016. Retrieved March 24, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Sousa, J. P. A., & Marques, V. (2019). Plano de Atividades 2019. Retrieved March 24, 2021, from http://www.ipst.pt/index.php/pt/planos-e-relatorios-de-atividades

Sousa, J. P. A., & Sousa, G. de. (2017). Plano estratégico IPST, IP: 2017-2019. Retrieved March 24, 2021, from http://www.ipst.pt/index.php/pt/planos-estrategicos

The New Yorker. (2021). The history of blood. Retrieved March 2, 2021, from https://www.newyorker.com/magazine/2019/01/14/the-history-of-blood

Tordecilla, R. D., Juan, A. A., Montoya-Torres, J. R., Quintero-Araujo, C. L., & Panadero, J. (2021). Simulation-optimization methods for designing and assessing resilient supply chain networks under uncertainty scenarios: A review. *Simulation Modelling Practice and Theory*, *106*(March 2020). https://doi.org/10.1016/j.simpat.2020.102166

Wang, K. M., & Ma, Z. J. (2015). Age-based policy for blood transshipment during blood shortage. *Transportation Research Part E: Logistics and Transportation Review*, *80*, 166–183. https://doi.org/10.1016/j.tre.2015.05.007

Williamson, L. M., & Devine, D. V. (2013). Challenges in the management of the blood supply. *The Lancet*, *381*(9880), 1866–1875. https://doi.org/10.1016/S0140-6736(13)60631-5

World Health Organization. (2010). Towards 100 % Voluntary Blood Donation: A Global Framework for Action. Retrieved October 20, 2020, from https://www.who.int/bloodsafety/publications/9789241599696/en/

World Health Organization. (2020). Data and statistics. Retrieved October 27, 2020, from https://www.euro.who.int/en/health-topics/Health-systems/blood-safety/data-and-statistics

World Health Organization. (2021). Blood safety and availability. Retrieved March 3, 2021, from https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability

Yang, Z., Tate, J. E., Morganti, E., & Shepherd, S. P. (2021). Real-world CO2 and NOX emissions from refrigerated vans. *Science of the Total Environment*, *763*(X), 142974. https://doi.org/10.1016/j.scitotenv.2020.142974

Zahiri, B., Torabi, S. A., Mousazadeh, M., & Mansouri, S. A. (2013). Blood collection management: Methodology and application. *Applied Mathematical Modelling*, *39*(23–24), 7680–7696. https://doi.org/10.1016/j.apm.2015.04.028

Zahiri, Behzad, & Pishvaee, M. S. (2017). Blood supply chain network design considering blood group compatibility under uncertainty. *International Journal of Production Research*, *55*(7), 2013–2033. https://doi.org/10.1080/00207543.2016.1262563

Appendix A

Table A1 - Comparative summary of work on blood SCND under uncertainty

Articles	Uncertain parameters		Time period		Echelon		Mathematical approach(es)	Solution approach(es)	Objective function(s)			Case study	Remarks
	Demand	Supply	Single	Multi	Single	Multi			Single	Bi	Multi		
Jabbarzadeh et al. (2014)	✓	✓		✓		✓	Stochastic programming		✓			✓	Disaster context
Ramezanian & Behboodi (2017)	✓			✓		✓	Robust optimisation	Exact methods	✓			✓	Social aspects
Fahimnia et al. (2017)	✓	✓		✓		✓	Stochastic programming	Exact methods		✓		✓	Disaster context
Zahiri & Pishvaee (2017)	✓	✓		✓		✓	Fuzzy programming Robust optimisation	Exact methods		✓		✓	Blood group compatibility
Heidari-Fathian & Pasandideh (2018)	✓	✓		✓		✓	Robust optimisation	Exact methods			✓		Green/ environmental SCND paradigm
Habibi-Kouchaksaraei et al. (2018)	✓			✓		✓	Robust optimisation	Exact methods		✓		✓	Disaster context
Eskandari-Khanghahi et al. (2018)	✓	✓		✓		✓	Fuzzy programming	Exact methods Metaheuristics			✓		Sustainable SCND paradigm
Samani et al. (2019)	✓	✓		✓		✓	Robust optimisation	Exact methods			✓	✓	Qualitative attributes
Hamdan & Diabat (2020)	✓	✓		✓		✓	Stochastic programming	Exact methods		✓		✓	Resilient SCND paradigm
Haghjoo et al. (2020)	✓			✓		✓	Robust optimisation	Metaheuristics	✓			✓	Disaster context
Arani et al. (2021)	✓	✓		✓		✓	Stochastic programming	Exact methods			✓		Sustainable lateral resupply problem

Appendix B

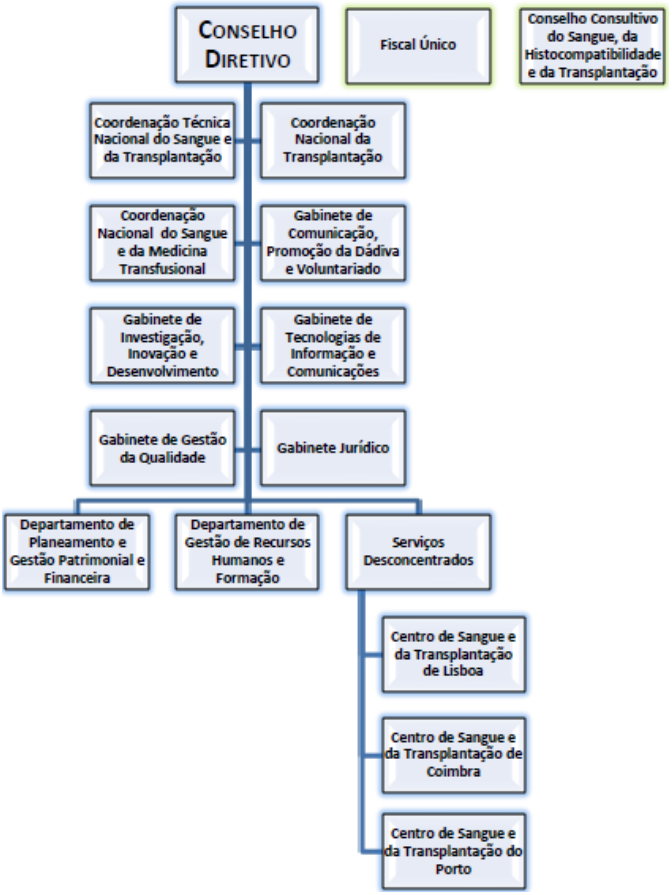

Figure B1 - IPST organisation chart. Source: Escoval & Marques (2020a)

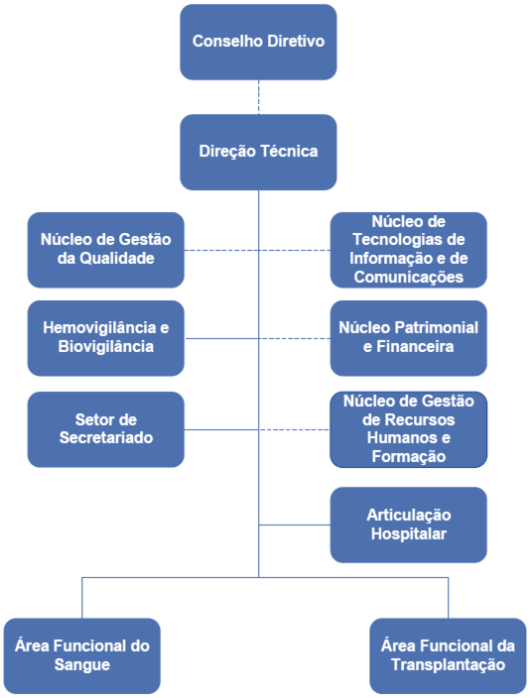

Figure B2 - Organisation chart of the CSTs. Source: J. P. A. Sousa & Sousa (2017)

Appendix C

Table C1 - Hospital blood units in Portugal. Source: Escoval et al. (2020); Araújo et al. (2020)

Region	Hospital blood units	Collection	Testing and processing
North	Hospital São João – Centro Hospitalar Universitário de São João, EPE	✓	Unknown
	Centro Hospitalar Universitário do Porto, EPE	✓	Unknown
	Unidade Hospitalar de Famalicão – Centro Hospitalar do Médio Ave, EPE	✓	Unknown
	Centro Hospitalar Vila Nova de Gaia/Espinho, EPE	✓	Unknown
	Instituto Português de Oncologia do Porto, EPE	✓	Unknown
	Hospital de Santa Luzia (Viana do Castelo) – Unidade de Saúde Local do Alto Minho, EPE	✓	Unknown
	Hospital de Braga, EPE	✓	Unknown
Centre	Hospital Pêro da Covilhã – Centro Hospitalar Universitário Cova da Beira, EPE	✓	Unknown
	Centro Hospitalar e Universitário de Coimbra, EPE	✓	Unknown
	Hospital São Teotónio – Centro Hospitalar Tondela-Viseu, EPE	✓	Unknown
Lisboa e Vale do Tejo	Hospital de São José – Centro Hospitalar Universitário Lisboa Central, EPE	✓	Unknown
	Centro Hospitalar de Setúbal, EPE	✓	Unknown
	Hospital de Torres Novas – Centro Hospitalar Médio Tejo, EPE	✓	Unknown
	Hospital Professor Doutor Fernando Fonseca, EPE	✓	✓
	Hospital Garcia de Orta, EPE	✓	✓
	Instituto Português de Oncologia de Lisboa, EPE	✓	✓
	Hospital de Vila Franca de Xira, PPP	✓	✓
	Centro Hospitalar Barreiro/Montijo, EPE	✓	Unknown
Alentejo	Hospital do Litoral Alentejano – Unidade Local de Saúde do Litoral Alentejano, EPE	✓	Unknown
	Hospital Espírito Santo de Évora, EPE	✓	✓
	Hospital Santa Luzia de Elvas – Unidade Local de Saúde do Norte Alentejano, EPE	✓	Unknown
	Hospital Distrital de Portalegre – Unidade Local de Saúde do Norte Alentejano, EPE	✓	Unknown
	Hospital de Beja – Unidade Local de Saúde do Baixo Alentejo, EPE	✓	✓
Algarve	Hospital de Faro – Centro Hospitalar Universitário do Algarve, EPE	✓	Unknown
	Hospital de Portimão – Centro Hospitalar Universitário do Algarve, EPE	✓	Unknown

Appendix D

Table D1 - Donor group locations

District	Municipality/Donor group
Aveiro	São João da Madeira
Braga	Braga
Coimbra	Coimbra
Faro	Olhão
Leiria	Peniche
Lisboa	Amadora
Porto	Porto
Santarém	Entroncamento
Setúbal	Almada
Viana do Castelo	Viana do Castelo
Vila Real	Peso da Régua
Viseu	Viseu

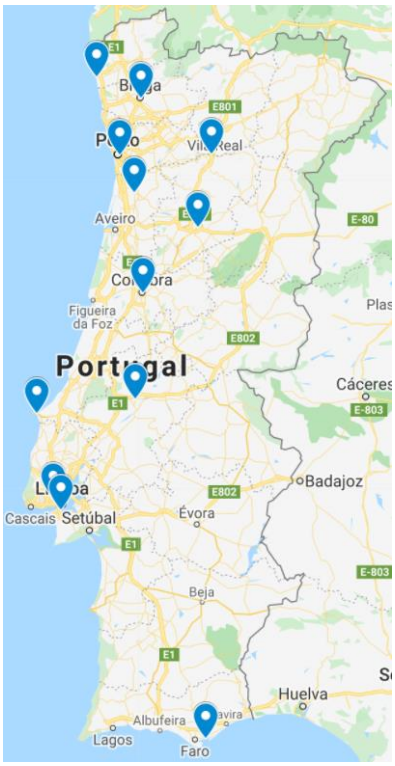

Figure D1 - Geographical distribution of donor groups

Table D2 - Fixed blood collection unit locations

District	Fixed blood collection unit	Existing	Candidate
Aveiro	São João da Madeira		✓
Braga	Braga	✓	
Coimbra	Coimbra	✓	
Faro	Faro	✓	
Leiria	Peniche		✓
Lisboa	Lisboa	✓	
Porto	Porto	✓	
Santarém	Santarém	✓	
Setúbal	Setúbal	✓	
Viana do Castelo	Viana do Castelo	✓	
Vila Real	Peso da Régua		✓
Viseu	Viseu	✓	

Figure D2 - Geographical distribution of fixed blood collection units

Table D3 - Blood centre locations

Blood centres	Existing	Candidate
Aveiro		✓
Braga		✓
Coimbra	✓	
Faro		✓
Leiria		✓
Lisboa	✓	
Porto	✓	
Santarém		✓
Setúbal		✓
Viana do Castelo		✓
Vila Real		✓
Viseu		✓

Figure D3 - Geographical distribution of blood centres

Table D4 - Mobile blood collection unit locations

District	Municipality/Mobile blood collection unit
Aveiro	Sever do Vouga
Braga	Celorico de Basto
Coimbra	Oliveira do Hospital
Faro	Tavira
Leiria	Bombarral
Lisboa	Oeiras
Porto	Marco de Canaveses
Santarém	Ferreira do Zêzere
Setúbal	Seixal
Viana do Castelo	Ponte de Lima
Vila Real	Alijó
Viseu	Armamar

Figure D4 - Geographical distribution of mobile blood collection units

Table D5 - Demand node locations

District	Municipality/Demand node
Aveiro	São João da Madeira
Braga	Braga
Coimbra	Coimbra
Faro	Portimão
Leiria	Peniche
Lisboa	Amadora
Porto	Porto
Santarém	Torres Novas
Setúbal	Almada
Viana do Castelo	Viana do Castelo
Vila Real	Vila Real
Viseu	Viseu

Figure D5 - Geographical distribution of demand nodes

Appendix E

Table E1 - Performance measures of the deterministic and stochastic approaches of the Lisboa e Vale do Tejo case

Performance measure			Deterministic approach	Stochastic approach		
				S3	S4	S6
Capacity utilisation rate (%)	Collection (fixed blood collection units)		13.24	13.53	12.42	13.16
	Collection (blood centres)		62.85	62.98	56.17	56.45
	Production (blood centres)	RBC	40.70	40.56	35.75	36.02
		PLT	57.99	59.80	56.29	57.38
Service level (%)	RBC	AB+	59.95	54.54	29.98	34.09
		AB–	-	-	-	-
		A+	68.69	61.47	61.37	53.78
		A–	62.17	59.55	56.52	51.78
		B+	60.58	52.78	53.85	49.67
		B–	-	-	-	-
		O+	65.83	60.36	58.38	56.41
		O–	62.02	56.87	52.72	45.50
	PLT	AB+	100	90.62	91.78	94.72
		AB–	99.37	54.05	93.04	76.76
		A+	99.94	94.30	97.22	89.90
		A–	100	97.38	100	97.42
		B+	99.95	97.43	98.96	96.33
		B–	100	93.75	97.74	96.64
		O+	100	94.36	97.77	87.15
		O–	100	94.31	97.45	98.82

(Continued)

Performance measure			Deterministic approach	Stochastic approach		
				S3	S4	S6
Wastage (%)	RBC	AB+	-	-	-	-
		AB–	-	-	-	-
		A+	-	-	-	-
		A–	-	-	-	-
		B+	-	-	-	-
		B–	-	-	-	-
		O+	-	-	-	-
		O–	-	-	-	-
	PLT	AB+	-	-	-	0.24
		AB–	-	-	-	-
		A+	1.21	-	-	-
		A–	-	-	-	-
		B+	0.10	0.94	0.05	-
		B–	-	-	-	-
		O+	0.02	-	-	-
		O–	1.05	-	-	-
Substitutability (%)	RBC		-	-	-	-
	PLT		1.95	2.50	2.60	1.65