UNIVERSITY OF SOUTHAMPTON

FACULTY OF BUSINESS, LAW AND ART

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Improving the Blood Supply Chain: Simulation and Optimisation Models to Support Collection, Production and Location-Allocation Decisions

by

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ABSTRACT

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IMPROVING THE BLOOD SUPPLY CHAIN: SIMULATION AND OPTIMISATION MODELS TO SUPPORT COLLECTION, PRODUCTION AND LOCATION-ALLOCATION DECISIONS

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This thesis introduces and studies different problems in the blood supply chain. The problems are focused on aspects less frequently studied in the literature such as the exploitation of the different collection and production alternatives, consideration of multiple products and uncertainty in demand and supply. These important features can be found in different decision levels, including daily collections, annual planning and at the strategic level when the blood supply chain is designed. For each problem presented, a suitable solution strategy is proposed. Different methods such as discrete event simulation, Monte Carlo simulation, optimisation, stochastic optimisation and multi-objective optimisation have been used to provide solutions to the problems studied. A simulation-optimisation model to support collection and production decisions in the blood supply chain is first presented. A model which integrated discrete event simulation and integer linear programming was designed to solve this problem. The model is tested using data from a blood centre in Colombia. Results show that key performance indicators such as total cost, number of donors, shortage and outdated units are improved by using the approach proposed. In addition, a stochastic multi-objective optimisation model to study the trade-off between cost and number of donors required is also included in this thesis. This model supports the decision of number of donors required by using whole blood and aphaeresis collection processes as well as considering the different blood groups and two main objectives: minimisation of cost and donors. The problem is solved using

a combination of the augmented epsilon-constraint algorithm and the sample average approximation technique. A Pareto front considering stochastic demand is obtained by applying the proposed method. The final model included studies the optimal design of a blood supply chain as well as a discussion about the main motivations for centralised and decentralized systems. A stochastic mixed integer linear programming model is proposed and a solution method based on the sample average approximation technique is designed to address the problem. The complete approach is applied to a case study and several scenarios are generated to evaluate different travel time policies as well as the impact of using aphaeresis processes.

Keywords Operational research; blood supply chain; blood collection; optimisation; simulation; aphaeresis.

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Declaration of Authorship

I, Andres Felipe Osorio Muriel , declare that the thesis entitled *Improving the Blood Supply Chain: Simulation and Optimisation Models to Support Collection, Production and Location-Allocation Decisions* and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published as:
  - Osorio, A.F., Brailsford, S.C. and 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.

– Osorio, A.F., Brailsford, S.C., Smith, H.K., Forero, S.P., Camacho, B. (2016). Simulation-optimization model for production planning in the blood supply chain. *Health Care Management Science*.[Online].
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– Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2014). A stochastic optimisation model for technology selection and donor assignment in the blood supply chain. EURO Working Group on Operational Research Applied to Health Services Conference: ORAHS 2014. Lisbon, Portugal

– Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2015). Simulation-optimisation model for production planning in the blood supply chain. EURO Working Group on Operational Research Applied to Health Services Conference: ORAHS 2015. Montreal, Canada.

– Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2015). Simulation-optimisation model for production planning in the blood supply chain. In European Conference for Operational Research: 27th EURO Conference. Glasgow, Scotland.

– Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2015). A multi-objective stochastic optimisation model for technology selection and donor assignment in the blood supply chain. EURO Working Group on Operational Research

for Development Workshop: EWG-ORD IFORS OR For development workshop 2015. Glasgow, Scotland.

- Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2016). Simulation-optimisation model for production planning in the blood supply chain. In Escuela Latino-Iberoamericana de Verano de Investigacion de Operaciones: ELAVIO 2016. Cali, Colombia.
- Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2016). Designing the blood supply chain: a location-allocation model with collection and production considerations. EURO Working Group on Operational Research for Development Workshop: EWG-ORD IFORS OR For development workshop 2016. Poznan, Poland.
- Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2016). Designing the blood supply chain: a location-allocation model with collection and production considerations. EURO Working Group on Operational Research Applied to Health Services Conference: ORAHS 2016. Pamplona, Spain.
- Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2016). Designing the blood supply chain: a location-allocation model with collection and production considerations. In European Conference for Operational Research: 28th EURO Conference. Poznan, Poland.

Signed:

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Date:

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En memoria de mi padre, Yecid Osorio.

Dedico esta tesis con todo mi amor y eterno agradecimiento...

a Dios mi creador,

a mi amada esposa Rosmery Linares,

a mi madre Vitelma Muriel,

y a mi hermana Martha Osorio.

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With the oversight of my main supervisor, editorial advice has been sought. No changes of intellectual content were made as a result of this advice.

List of Abbreviations

ARC	American Red Cross
CBS	Canadian Blood System
DES	Discrete event simulation
INS	Instituto Nacional de Salud
ILP	Integer Linear Programming
MILP	Mixed Integer Linear Programming
PAHO	Pan American Health Organization
RBCs	Red blood cells
SAA	Sample Average Approximation
WHO	World Health Organization

Chapter 1

Introduction

1.1 Introduction to the Study

The blood supply chain is present in almost every country in the world. Different types of networks exist, including public, private and hybrid systems, as well as centralised and decentralised topologies. In addition, different types of resources, collection strategies and production technologies can also be found. However, the main goal is basically the same: to collect and produce enough blood products to meet the demand. This all means that decision-making for the blood supply chain is challenging, given the increasing demand for blood products, the decreasing population of donors (Seifried et al. 2011) and the uncertainty present in demand and supply. The problem is even more complex in developing countries where the donation rate is lower. Given this, advanced techniques for decision making are required in order to make better use of resources available. This research aims to study different aspects of the blood supply chain, such as the state of the art and research opportunities, as well as production planning, collection strategy and location-allocation problems, using the data sets of real systems. The thesis is presented as a "three-paper" thesis (actually, four papers) where Chapters 2, 3, 4 and 5 each contain a separate research paper. The first two papers have already been published, the third is under review and the fourth was recently submitted.

This supply chain can be split into four main stages: collection, production, inventory and distribution. Collection is responsible for the recruitment of donors and to collect the blood and blood products; production separates the whole blood into sub-products and carries out quality tests. The inventory stage stores the final products to be used, and finally, distribution is responsible for transporting the product to the transfusion points. Whole blood is collected mostly from voluntary donors; however, in some countries including the USA, blood is also collected from paid donors. The most common collection method is whole blood donation, which consists of extracting approximately 450 ml of blood using a set of collection bags. The blood is centrifuged and, depending on the settings for speeds and processing times, different components such as red blood cells (RBCs), platelets, cryoprecipitate and plasma can be obtained. This process is known as fractionation. Each product is used for different treatments: for instance, RBCs are required for the treatment of anaemia and massive blood loss, whereas platelets are

required for cancer patients and plasma is required to treat patients with burns. These are only examples, since each component can have multiple uses. On the other hand, aphaeresis processes, which directly extract a single blood component from a donor, are considerably more efficient than fractionation. However, this type of process also has disadvantages, such as a higher cost and longer collection time.

Given the extensive use of blood products, their availability becomes critical, since lives can be lost if no stock is available when it is needed. Moreover, blood is collected only from human donors, and blood donation rates vary between different countries and also within countries. According to the World Health Organisation (WHO 2014), approximately 108 million blood donations were collected worldwide in 2012. However, significant differences can be identified in countries with different income levels. The median blood donation rate in high-income countries is 36.8 donations per 1000 population. However, this value decreases to 11.7 donations in middle-income countries and 3.9 donations in low-income countries. One of the reasons for these differences is the need to develop an infrastructure for collecting, processing and distributing blood and its products, to collect and process enough blood to meet the demand. In addition, many other factors such as comfort, risk, convenience and accessibility can affect the decisions of individuals to donate, which increase the required effort for collection. Nevertheless, the blood supply chain in each country is defined according to national blood strategies, which means that different schemes and degrees of centralisation can be found around the world. Developed countries such as the UK, Canada and Australia have developed highly centralised blood networks. On the other hand, examples of decentralised and mixed systems can be found in developing countries, from internal blood banks in hospitals, to multiple collection, processing and distribution centres that supply several demand points.

Special features of the blood supply chain must be taken into account at the moment of fulfilling demand. Factors such as blood type, compatibility, different shelf lives of blood products and crossmatching add complexity to blood supply chain systems and the decision-making process. There are eight main blood groups (A, B, AB and O, each of which can be rhesus-positive or -negative), and each group is present at differing

frequencies in different populations, with variations between ethnicities and geographical regions. Figure 1.1 depicts the percentage frequency of blood groups for both the UK and Colombia, according to Katsaliaki & Brailsford (2007), and Beltran et al. (1999), respectively.

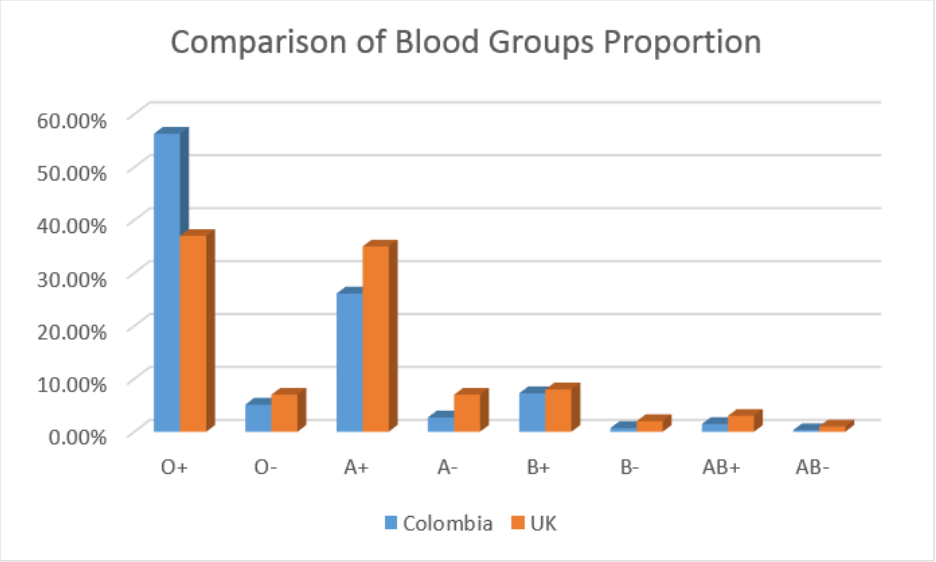


Figure 1.1: Blood groups proportions in the UK and Colombia.

Because some blood types are very rare, the use of substitute products is often required. This process is called mismatching and there are specific restrictions and preferences that regulate their use. Appendix C presents the compatibility tables for each product.

The perishability of blood products is another important factor to be considered; the shelf-life differs for platelets, RBCs, plasma, and cryoprecipitate. Platelets are the most critical component, with a shelf-life of only five days, followed by RBCs with 42 days, and finally, plasma and cryoprecipitate which can be stored for up to one year. Some procedures also require "fresh" products instead of "old" products, which increases the complexity of inventory management. Furthermore, a blood product that has not been transfused before the end of its shelf-life must be discarded. Blood production and inventory planning are extremely important, since blood products are not produced independently; there are different primary fractionation alternatives that generate from one to four products, as well as different methods of collection.

Crossmatching is the process that checks the compatibility between donor and patient and this is carried out in two different ways. The first method is called type and screen (T&S) and consists of computer-aided checking, i.e. software analyses the results of previous tests for the product and defines the most suitable product to be transfused. This method has the advantage that the product is already available in the inventory. The second method consists of physically removing the product from the shelves and developing a physical test. This means that the product is not available in the inventory during a time-period called the crossmatching release period. Since the probability of transfusion (the crossmatching rate) is usually low, the product is often returned to the inventory with a shorter remaining shelf-life. Longer crossmatching release periods and low crossmatching rates increase the outdating rate indicator.

The blood supply chain was a very active research topic in Operational Research in the 1970s and 1980s; however, interest in this research area decreased in the 1990s. The main reason, according to Pierskalla (2005) was the cut in research budgets for this type of project. However, based on the number of published papers in the last ten years, the interest has been increasing considerably. Figure 1.2 shows the number of publications that contain quantitative models relating to the blood supply chain.

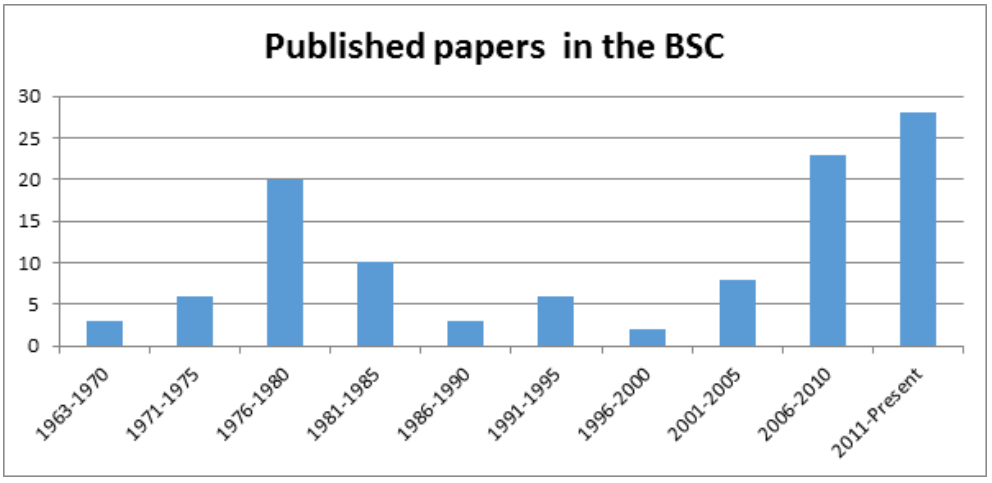


Figure 1.2: Published papers containing quantitative models in the blood supply chain. Source: Osorio et al. (2015)

Despite the rise in the number of papers, some areas have received less attention. As previously mentioned, the blood supply chain can be split into four stages: collection, production, inventory and distribution. The main interest has focused on inventory

policies and the least-studied stage is production. Some publications have considered several echelons, termed integrated models. Figure 1.3 shows the number of papers in each category.

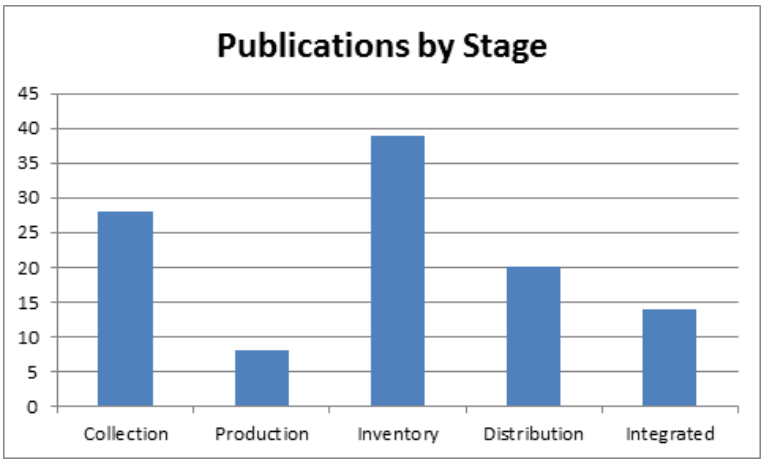


Figure 1.3: Published papers by stage in the blood supply chain. Source: Osorio et al. (2015)

A complete analysis of the literature is presented in Chapter 2 and by Osorio et al. (2015) who identify several gaps in the literature of the blood supply chain and propose a decision-making framework to categorise decisions according to the stage and hierarchical level.

1.2 Motivation for this Research

The author of this thesis is from Colombia and while working in a Colombian university he collaborated with a large blood centre in the city of Cali, Colombia. The problems of the blood supply chain in Colombia and other developing countries stimulated his initial interest in this area.

The Colombian National Blood Bank Network is comprised of 82 blood banks and 414 points for transfusion services (INS 2016). Blood banks differ in size and types of services offered. Large public and private blood centres supplying products for several hospitals can be found in the large cities. Blood banks are also located within hospitals. The distribution centres are usually co-located with the blood banks. The Colombian system is highly decentralised, compared, for example, with the UK National Blood

Service network, which consists of five large production centres and 15 stock holding units across the country (Woodget 2014). Another feature of the Colombian system is the range of collection strategies across the country; each region defines the collection goals for blood and blood products using local decision rules. The highest proportion of platelets collected by aphaeresis in 2012 is represented by the Valle del Cauca region with 93%, followed by Antioquia with 42%. However, most regions collect platelets from whole blood donations. On the other hand, the highest proportion of RBCs produced using aphaeresis processes is represented by the Tolima region with 8.24%, followed by 6.26% from Bogota. Again, most regions obtain RBCs exclusively from whole blood donations.

Given all this, the study and solution of multiple problems from this particular system in different levels are the main motivation for this research. For independent blood centres, problems in collection and production planning need to be studied including tactical decisions such as the structure of the collection including aphaeresis and whole blood as well as operational decisions such as numbers of donors required and fractionation decisions. At a different level, for a local or national blood network, decisions in terms of configuration of the network, as well as collection and fractionation strategies by region also need to be studied.

In summary, the motivation for this research is to propose models and approaches to support the decision making process in the blood supply chain. The path of development of this research has been motivated by the Colombian blood supply chain. However, the problems studied here arise in all blood supply chains and have been identified as gaps in the blood supply chain literature.

1.3 Research Aims, Objectives and Contributions

The main features of blood groups, compatibility, shelf-life and the four main stages are common to most blood supply chains. However, each system possesses particularities due to policies or specific conditions. These specific conditions might include centralisation aspects, purchase or production decisions and geographical conditions, as

well as policies concerning blood returns, mismatching, and crossmatching. The models in the literature are usually designed for specific applications; however, some of these models are adaptable to other systems. The models included in this research are also designed for the blood supply system in Colombia, but they retain the main features of typical blood supply chains and are readily applicable to other blood supply chains. The Colombian blood supply chain is highly decentralised and operates under several schemes, including public and private blood banks and blood centres.

Broadly, the research in this thesis aims to develop a decision-making framework and apply operational research methods to analyse and improve the blood supply chain. Furthermore, the research mainly focuses on the study of blood centres that comprise the Colombian blood supply chain.

This research pursues the following objectives:

- To provide an updated review of quantitative models in the blood supply chain.
- To provide a decision-making framework for each stage in the blood supply chain.
- To develop a simulation model to represent the different stages of the blood supply chain, considering collection and production decisions.
- To develop an integrated simulation-optimisation framework to support production decisions in the blood supply chain.
- To develop a mathematical model to support the definition of the collection strategy in the blood supply chain.
- To develop a mathematical model to support the design of a blood supply chain, including location, allocation, collection, production and distribution decisions.
- To extend the state of the art in the blood supply chain by including production decisions, multiple products and multiple collection alternatives.
- To develop a decision support tool for policy makers, considering the specific conditions in Colombia.

The main contributions to knowledge of this research are listed as follows:

- A structured review and a taxonomic framework to study blood supply chain problems.
- A robust simulation-optimisation methodology to support production decisions in the blood supply chain.
- The inclusion in modelling of multiple aspects not considered in previous research, such as collection and production alternatives and collection and demand behaviour.
- An innovative integration of multi-objective and stochastic methodologies to support the definition of the collection strategy in the blood supply chain.
- The identification of the features that define the production planning, collection strategy and location-allocation problems, as well as models that include objectives, decision variables, parameters, constraints, and robust solution methods.

1.4 Methodology

This thesis studies several problems; for each problem a different approach has been used. Furthermore different sources of information have been consulted to develop the case studies presented here. The information used includes primary data as interviews and secondary data for one of the chapters and just secondary data for the rest of the chapters. In this section a general description of methods, data used and ethical approval is presented.

Several operational research techniques are used in this thesis. Firstly an integration of discrete event simulation and integer linear programming is developed to solve the problem presented in Chapter 3. In this integration, the optimisation model is embedded in the simulation model and is run every day. Both models interchange information in a daily basis. This combination is classified as "Iterative Optimization-based Simulation (IOS)" according to the taxonomy proposed in Figueira & Almada-Lobo (2014).

In Chapter 4, the multi-objective technique called Epsilon-constraints is integrated with the stochastic optimization method sample average approximation (SAA). The Epsilon-constraint algorithm converts one of the objective functions into a constraint and sets a limit called Epsilon (in our case it is an upper limit). In the integrated algorithm a SAA problem is run for different maximum values of epsilon, obtaining the Pareto front of the stochastic multi-objective problem.

Finally, in the model presented in Chapter 5, the algorithm SAA is also used. However, the complexity of this model is greater than that of the previous chapter, and the model cannot be solved using only a solver. In order to address this, a heuristic based on the SAA method is proposed. This heuristic solves the SAA problem in a different way from the original method: instead of solving all the scenarios simultaneously, the heuristic solves each scenario individually. After this, "good" and "bad" locations are identified according to the number of appearances in the individual scenarios. These "good" and "bad" locations are fixed and the SAA problem is solved considering all the scenarios simultaneously.

All the optimisation models presented in this thesis were coded in Java and solved using the Java interface of Gurobi 5.6.3. In addition, all the algorithms developed were also written in Java.

Different data sources were accessed during the development of this thesis. The data used for the model presented in Chapter 3 included semi-structured interviews with personnel of the Hemocentro Distrital in Bogotá Colombia, as well as secondary data obtained from the information system and historical reports of the Hemocentro. The information used in the model did not include personal data. In general terms the data used in this model corresponds to collection, production, demand and costs. Data used in the models presented in Chapters 4 and 5 relates to collection, demand, and distances, and is publically available on websites.

The research described in Chapter 3 was given ethical approval by the University of Southampton with ERGO submission number 12251. The data used in Chapters 4 and 5, is secondary data aggregated at a non-human level and is publically available. Given this, ethics approval was considered not to be needed for this part of the research.

1.5 Overview of Problems Studied and Models

This section gives a detailed overview of the thesis and demonstrates that the problems in the blood supply chain are studied in a coherent manner. Table 1.1 gives a summary of the papers according to the different aspects of the blood supply chain and models. Modelling in the thesis starts in Chapter 3 at both the strategic and the operational level of collection and production planning for a single blood centre. The model presented in Chapter 4 supports tactical and strategic decisions on blood collection for one blood centre or in a region. Finally, in Chapter 5, strategic problems on location blood supply chain facilities in an entire country are studied, with a focus on centralisation versus decentralisation. Details on the individual problems and information on the types of model developed, decision variables, decision levels and solution methods are presented in the following sections.

Table 1.1: Chapter summary

Chapter/ Title	**Levels/ planning horizon**	**Decisions**	**Echelons modelled**	**Solution approach**	**Application area**	**Case study data**
3 "Simulation-optimisation model for production planning in the blood supply chain"	Strategic and/or operational/ 7-day planning horizon (or months)	Daily numbers of blood units by blood group to be collected and how to fractionate the blood collected	Collection, production, inventory and distribution	Simulation/optimisation	A single blood centre	Daily demand data from the Hemocentro Distrital blood centre in Bogotá, Colombia
4 "Whole blood or aphaeresis donations? A multi-objective stochastic optimization approach"	Tactical and strategic/ one-year planning horizon	Numbers of pieces of equipment required for each collection method; aggregated collection and fractionation strategy	Collection, production, inventory	Stochastic multi-objective optimisation model – a combination of the augmented epsilon-constraint and the Sample Average Approximation (SAA) algorithms	A blood centre or a region	Demand over a one-year period from Bogotá, Colombia
5 "Designing the blood supply chain: how much, how and where?"	Strategic/- costs estimated over a one-year period	Location and capacity of collection, production and distribution centres; also numbers of donors and collection and fractionation strategies	Collection, production, inventory and distribution	Stochastic mixed integer linear programme – SAA heuristic solution method	A country's blood supply chain	National data on yearly demand by region from the Colombia blood system

1.5.1 The Production Planning Problem

The daily operation of the blood supply chain consists of recruiting donors, collecting blood and blood products, fractionation processes and inventory management. This means that daily decisions concerning the number of blood units to collect and how to fractionate the blood collected must be made. However, these decisions depend on multiple factors such as inventory levels, donations on previous days, the patterns of the demand and donations for each day of the planning horizon. In addition, indicators such as outdating and shortage rates are also directly affected by collection and production decisions. These decisions include the type of collection kits that should be used, which blood groups are immediately required and which of these can be deferred as well as which fractionation process should be carried out.

Chapter 3 presents a simulation-optimization model to support collection and production decisions in the blood supply chain. This model can be used to support strategic decisions on capacity provided for collection as well as operational decisions on collection and fractionation alternatives. The model can be applied to individual blood centres. The collection, production, inventory and distribution stages are modelled using discrete event simulation (DES); in addition an optimisation model is embedded and called on a daily basis in the simulation model. The decision variables of the optimization model are mainly related to the number of donors required by blood group and type of collection method. The constraints considered include demand satisfaction, blood proportions, capacity of collection among others. The model seeks to improve the most relevant indicators of the blood supply chain such as cost, stockouts, outdated units, and number of donors. This model is applied to a case study that uses real data from the Hemocentro Distrital in Bogotá, Colombia. Probability distributions are fitted using one year's data on daily donations and demand.

1.5.2 The Collection Strategy

The two collection methods currently available in the blood supply chain are whole-blood collection and aphaeresis collection, which use different equipment. Whole-blood

collection uses phlebotomy (the process of making an incision in a vein with a needle) and a set of bags to collect approximately 450 ml of blood. The extracted blood unit is then taken into the production stage, where centrifugation is performed to obtain the different components. In contrast, the aphaeresis procedure extracts the blood from the donor, but the blood is processed in real time, using equipment that withdraws the desired component (RBCs, plasma, platelets) and returns the remaining fluid to the donor. The collection kits to carry out aphaeresis collection are considerably more expensive than the sets of bags for whole-blood donation. However, aphaeresis processes are more efficient than whole-blood donation, since several units of the same product can be obtained; for example, two units of RBCs can be obtained using aphaeresis, or up to 12 standard units of platelets. The products obtained from both processes are substitutable; however, the choice of either method depends on the policies and strategies defined by clinical staff. Most studies on collection are based on whole-blood donation. However, it is also necessary to consider the different alternatives and features in terms of efficiency and cost, to define the collection strategy. Finally, demand is an uncertain condition in most supply chains, including the blood supply chain. The choice of collection strategy depends mainly on the structure of demand, i.e. how much product of each type is ordered.

Chapter 4 presents a stochastic multi-objective optimisation model to study the two collection methods, considering the different blood groups and trade-offs between the two main objectives: minimisation of cost and donors. This problem is aimed at supporting tactical decisions such as numbers of equipment required for each collection method, as well as the aggregated collection and fractionation strategy over a one-year planning horizon. The model is applicable to independent blood centres or can be easily extended to a blood network. This problem is modelled as a two-stage optimization problem where the first stage decision variables are the purchase of equipment decisions and the second stage decision variables are the number of donors required, collection and fractionation alternatives as well as the use of substitute products. This model is developed using demand over a one-year period from Bogotá, Colombia. In order to solve the problem, a novel combination of the augmented epsilon-constraint and the Sample Average Approximation (SAA) algorithms is developed.

1.5.3 The Location – Allocation Problem

Different topologies of the blood supply chain can be found around the world. The design of the network might depend on factors such as geography, policies, costs, and service levels; however, developed countries have aimed to centralise facilities such as production centres. This centralisation has occurred together with the creation of distribution centres, to maintain the service level, as well as meeting distance and time constraints. A large body of literature exists concerning location-allocation problems in general; however, only few publications deal with the blood supply chain. Furthermore, some location-allocation models in the blood supply chain have not considered important aspects, such as collection and production alternatives and multiple products that might have an impact on the optimal design of the network. Moreover, the design of the blood supply chain should also consider the specific constraints of the system analysed, such as geography, available technologies and policies.

Chapter 5 studies the optimal configuration of a country's blood supply chain at a strategic level. This chapter presents the main motivations for centralised and decentralised systems and proposes a stochastic mixed integer linear programme (MILP) to support the design of the blood supply chain. In this model the decision variables are the location and capacity of collection, production and distribution centres. In addition, flow variables between the different stages are also modelled. As in the previous chapters, decisions on numbers of donors and collection and fractionation strategies are also included. The decisions supported by this model are strategic and can be used to design or redesign a blood supply chain under different policies. Constraints of the model consider demand satisfaction, capacity, and distance covering among others. In order to solve the model, the sample average approximation algorithm is used. However, given the complexity of the resulting model, a heuristic based on the SAA method is developed. This heuristic allows good solutions to be obtained. The model and solution approach are applied to a case study using national data from the Colombia blood system. Other sources of information are Google Maps, and previous studies published regarding the cost of the different blood supply chain facilities. Several scenarios are analysed for different travel time configurations as well as different percentages of aphaeresis collection.

This Chapter has been submitted for publication in the journal Transfusion. This journal reports on the latest technical advances, discusses opposing viewpoints regarding controversial issues, and presents key conference proceedings, in addition to blood banking and transfusion medicine topics. Because of the broad readership of this journal, we have excluded all the mathematical equations and these are presented in Appendix D.

1.6 Collaboration with Other Researchers

Chapter 3 has been developed together with staff from the Hemocentro Distrital Colombia; however, the input from the staff was exclusively limited to provision of data and clarification of aspects of the processes modelled. All the models, results and analysis have been developed solely by the author of this thesis.

Chapter 5 has been developed in collaboration with Dr John Blake from Dalhousie University in Halifax, Nova Scotia, Canada. Dr Blake holds an Adjunct Scientist position at Canadian Blood Services. His input to this chapter has been the section on the Canadian experience of moving from a decentralised to a more centralised system, and the provision of feedback from the point of view of an expert researcher in the subject. However, all the modelling and solution methods have been developed by the author of this thesis.

1.7 Structure of the Thesis

This thesis is structured as follows:

Chapter 1 includes the introduction and general background to the subjects covered in the papers and also summarises the objectives and research questions, as well as the structure of the document.

Chapter 2 contains the final version of the paper "A structured review of quantitative models in the blood supply chain: a taxonomic framework for decision making". This paper has been published in the *International Journal of Production Research* and

presents a complete review of the state of the art of quantitative models in the blood supply chain. In addition, it introduces a framework to analyse decisions in each stage.

Chapter 3 contains the final version of the paper "Simulation-optimisation model for production planning in the blood supply chain". This paper has been published in the *journal Health Care Management Science*. This research presents a discrete event simulation model integrated with an integer linear programming model to support decisions in collection and production planning.

Chapter 4 contains the paper "Whole blood or aphaeresis donations? A multi-objective stochastic optimization approach". This paper has been submitted to the *European Journal of Operational Research* and presents an optimisation model, which contains two objective functions as well as stochastic parameters. To deal with this problem, a combination of the epsilon-constraint algorithm and the Sample Average Approximation (SAA) has been developed. The data used to develop this model are available online and the model does not represent a specific blood centre, but is a general case study using aggregated information from Bogota, Colombia.

Chapter 5 contains the paper "Designing the blood supply chain: how much, how and where?". This paper has been submitted to the journal *Transfusion* and presents a stochastic optimisation model to design the blood supply chain. Decisions such as collection and production alternatives, location and capacity of collection, production and distribution centres as well as allocation decisions are considered and modelled. To deal with this problem a heuristic based on the SAA method is proposed.

Chapter 6 presents the summary of the main contributions by chapter, the limitation of the models developed, general directions for research in the blood supply chain and other outcomes from this thesis.

Chapter 2

A Structured Review of Quantitative Models in the Blood Supply Chain: A Taxonomic Framework for Decision Making

Abstract

This paper presents a structured review of the literature on quantitative modelling for the blood product supply chain. This is a widely-researched topic, dating back to the 1960s, and several other reviews have been published over the years. However, this paper presents new relevant information for researchers, not only by including more recent models but chiefly because of the structured way in which the models are presented. The models are broken down into five categories. The first four categories represent the four stages (echelons) in the supply chain: collection, production, inventory, and delivery. The final category contains "integrated" models which cover more than one stage. Each section (other than integrated models, which are treated slightly differently) contains two distinct elements. The first element is a diagrammatic representation of decisions and relationships, broken down by hierarchy level (strategic – tactical – operational). The second element is a text description of the main features, contributions and gaps found in the analysed models. An additional element for each section is available online, namely a searchable table describing specific features of each echelon, together with a taxonomic key to assist the reader.

2.1 Introduction

2.1.1 The Blood Supply Chain

The blood supply chain comprises the processes of collecting, testing, processing and distributing blood and blood products, from donor to recipient. Blood products are transfused to patients as part of routine medical treatments or surgical operations, and also in emergency situations. This means that availability of the right blood products is critical, since lives can be lost if no stock is available when it is needed. At the same time, blood is collected from human beings and the blood donation rate varies across different countries. According to ARC (2014) in the US only 10% of all eligible people actually donate blood, and the World Health Organization states that the figures for middle- and low-income countries are considerably lower (WHO 2014). This all means

that decision-making for the blood supply chain is challenging, given the increasing demand for blood products as well as the decreasing population of donors (Seifried et al. 2011). Another important factor is cost; although blood itself is donated voluntarily in developed countries, many costs are incurred along the way, such as labour, testing, fractionation (separating whole blood into sub-products, of which there is potentially a vast range), storage and distribution. In general, an efficient blood supply chain should meet demand while at the same time reducing wastage and minimising costs. However, the limited shelf life of most blood products imposes strict constraints on this highly complex supply chain, which considerably increase the risks of shortages and outdating. Given the relevance, features and complexity of the system, it is necessary to develop robust methodologies to support the decision-making process at all stages of the blood supply chain.

The real-world importance of the blood supply chain is self-evident, since human lives are at stake. The complexity of the supply chain is perhaps less obvious. According to Katsaliaki & Brailsford (2007), more than a hundred different products can be derived from blood, including products and sub-products, but red blood cells (RBC), plasma, platelets and cryoprecipitate are considered to be the most important. Red blood cells represent 63.4% of the total transfused products, followed by plasma at 17.8%, platelets at 13.6% and finally cryoprecipitate at 5% (DHHS 2013). Moreover these products can be processed to obtain sub-products such as irradiated or washed products for special treatments or as raw material for other products such as recombinant products.

Components are used in different situations: for instance, red blood cells are required in anaemia treatments, while platelets are required for cancer patients and plasma is required to treat patients with burns. This list represents one single example of the use of each component; however each component can have many uses in distinct processes in healthcare. On the other hand, collecting blood requires a constant effort; in countries where donation is voluntary, many factors such as comfort, risks, convenience and accessibility can affect the decision to donate. However, obviously, in order to meet demand enough blood must be collected. Matching supply with demand, in supply chain terminology, requires developing an infrastructure for collecting, processing and distributing

blood and its products. Different configurations of the blood supply chain can be found both in the real world and in the literature, from internal blood banks in hospitals to multiple collection and processing and distribution centres supplying several demand points. The strategy followed can vary according with healthcare policies in different countries. However the goal remains the same, i.e. satisfying demand for blood products at minimal cost and with minimal wastage. In addition, special features of blood and blood products must be taken into account. Factors such as blood types, compatibilities and different shelf lives of blood products add complexity to blood supply chain systems and the decision making process. There are eight main blood groups (A, B, AB and O, each of which can be rhesus positive or negative) and each group has a different proportion in the population. The proportions vary between ethnicities and geographical regions, for instance, in the UK the proportions of type O positive and AB negative are 37% and 1% respectively (Katsaliaki & Brailsford 2007) while in Colombia the same blood types represent 56% and 0.3% respectively (Beltran et al. 1999). Because there are some very rare blood types, very often the use of substitute products is required. However there are specific restrictions and preferences in using them. Moreover, the shelf life of blood products is another important factor to be considered; platelets, red blood cells, plasma, and cryoprecipitate have different shelf lives. Platelets are the most critical component with a shelf life of just 5 days, followed by red blood cells with 42 days and finally plasma and cryoprecipitate with one year. This means that if a blood product has not been transfused before the end of its shelf life, it must be discarded. Finally, it is important to note that blood products are not produced independently. There are different primary fractionation alternatives that generate from one to four products, as well as different methods of collection.

2.1.2 Previous Reviews, Overviews and Frameworks

The blood supply chain has motivated researchers since 1960. Indeed, research in this field has contributed greatly to the development of effective methods for the management of perishable inventory (Nahmias 1982). A significant part of the related literature was developed in the 1970s and 80s. Several reviews have been published covering

distinct aspects of the blood supply chain. The first framework to classify the whole blood inventory problem is presented in Jennings (1973). This early work presents the problem by hierarchy level (strategic – tactical – operational) and shows the impact of the application of different blood inventory policies. Pierskalla (1980) provide a detailed analysis of configurations of the blood supply chain in the US. This article also describes the functions and authority degree of each level. In a paper published in the same year, Page (1980*a*) reviews the computer software available at that time for supporting blood bank processes. This covers factors including origin, capacity, functionality, state of development and cost.

Some review articles focus on specific blood products. Blake (2010) presents an important overview and problem description of inventory of platelet concentrates. He introduces the problem from the point of view of producers and consumers, and then review the literature, ending with a short discussion of solution strategies. On the other hand, Stanger et al. (2012) describe the best practices in red blood cell inventory management. This article discusses the main models in the literature on this specific topic and presents the results of a study undertaken in the UK. An important finding is that good practices are related more with good training, electronic crossmatching and simple decision rules, rather than some of the complex algorithms proposed in the literature.

Nahmias (1982) provides a complete overview of the theoretical models in perishable inventory at that time. The models presented in this article are applicable to different types of perishable inventory; however, several examples are explicitly applied to blood stocks. The models are presented according to features such as type of demand, type of lifetime and queuing modelling approaches. Nahmias (2011) presents an updated review of this subject. This book also contains a specific chapter discussing the different models and approaches applied to the blood inventories problem. Prastacos (1984) presents a review discussing the main contributions from Operational Research to the blood supply chain. The model includes a general overview of the different stages and the kind of decisions in each of them. This review takes a similar approach to Nahmias (2011), although the number of papers and the model features presented in each article are not comparable.

In the last decade, Pierskalla (2005) and Lowalekar & Ravichandran (2014) published articles analysing the whole supply chain, describing advances and opportunities for further research. Pierskalla, one of the great pioneers in this field, provides a broad analysis including different network configurations, location, and allocation and distribution decisions as well as areas for further research such as donor scheduling, production planning, and distribution. Lowalekar & Ravichandran (2014) present a complete overview of the state of the art of blood banks in India. In their paper, the literature is classified according to type of decisions in the blood supply chain. However, their classification is fairly general, compared with the present review where several distinct features are identified in each stage.

Finally, Beliën & Forcé (2012) published a literature review of the blood supply chain, which covers papers published up to 2010. Beliën and Forcé cover very diverse aspects of the topic, not just quantitative models, and classify models in eight general categories without detail about specific features of the supply chain. There are significant differences between the Beliën and Forcé paper and this review, in addition to including papers published up to 2014. This review has a different focus; we only consider quantitative models, and we present the main features of each model according to the relevant supply chain echelon. This means, for example, that in the collection stage, 14 distinct features of collection processes are included. There are similar numbers of different features in the production, inventory management and distribution echelons.

2.1.3 Paper Selection Process

The selection criteria for this review fall into two main categories. Firstly, we include papers that consider quantitative models for any stage of the blood supply chain. Secondly, papers from other knowledge areas such as perishable inventory and multi-type production with explicit application to the blood supply chain are also included. The search process included research articles, executive reports, proceedings, thesis and reports that meet any of the two points mentioned previously, published between 1963 and September 2014.

2.2 Review

In order to help the reader and present the information in a structured way, the literature and analysis of the blood supply chain will be presented according to the main echelons of the blood supply chain depicted in Figure 2.1. In reality, the system is not as linear as this. It is a highly complex process, since blood is transported not only between blood centres and hospitals but also between blood centres, in countries where there are regional or even national systems. Generally, however, after the production stage blood products are transported from a blood centre directly to the hospitals it serves, based on each hospital's request for replenishment, and are then stored in the hospital's blood bank as "unassigned inventory" until needed for a named patient. In order to assign blood units to a donor, different procedures to check compatibility can be used. On the one hand, electronic crossmatching, also known as Type and Screen (T&S) procedures, consist of computer-aided checking. In this case, there is no "assigned inventory" for a specific patient. On the other hand, crossmatching is the process of checking that the recipient's blood is compatible with the donated blood: this is more complex than merely matching the ABO Rh groups. The blood is then assigned to that patient and becomes "assigned inventory". Frequently, more blood is crossmatched than is actually required, since many doctors prefer to err on the side of caution. The application of these policies depends on several factors such as antibodies found in the patient's blood, probability of transfusion and internal policies of the institutions. In terms of safety, according to Georgsen & Kristensen (1998) and Chow (1999) T&S is comparable to crossmatching procedures. However, the most important effect of electronic crossmatching is in the performance of the blood bank. Blood units are always "at hand" inventory and can be used to transfuse other patients. This decreases the probability of expiration of a unit and helps blood managers to control inventories better, as well as decreasing stock out probabilities. Using crossmatching, unused blood can be returned to the hospital blood bank, although not normally to the distribution centre. Different countries have different returns policies, and these may also vary by blood group. An additional complication is mismatching, where patients can be transfused blood of a different type to their own: this can be done in emergency situations or to improve inventory planning

in small institutions where the rarer blood types are less frequently required. Again, there are many different policies for this. Thus "Distribution" occurs at least twice: it covers transportation of processed products from blood centres to hospital blood banks (or indeed other blood centres), as well as from the hospital blood bank to the operating room, care unit or ward where the recipient is located. Similarly, "Inventory" covers storage at blood centres and also within hospital blood banks, both assigned and unassigned. We have used the simplistic framework in Figure 2.1 as a helpful means for categorising the models, but in practice the third and fourth stages are intertwined. This of course greatly adds to the complexity of the blood supply chain in the real world, and the challenges of modelling it.

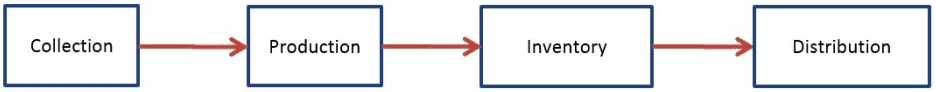


Figure 2.1: Echelons of the blood supply chain.

2.2.1 Collection

The collection stage comprises the processes of procurement of blood and blood products. This is the first echelon of the blood supply chain and its purpose is to obtain the quantity of blood and blood products required to meet demand. Decisions in this stage are mainly related to the management of blood collection: location and capacity decisions, collection methods and donor management. Figure 2.2 presents a schematic representation of the decisions in this stage. Decisions at the top of the figure are strategic, with tactical decisions in the middle and operational decisions at the bottom. Relationships between decisions are represented by blue arrows. The flow depicted in the bottom of the figure is the general process in the collection stage; this flow is represented by red arrows and the inputs/outputs are represented by grey boxes. Typically, blood is collected at donor centres, which can be at either fixed or mobile locations, and is then transported back to a processing and testing facility (a "blood centre") and is stored there awaiting onward distribution. In most cases whole blood is collected from donors, but occasionally a process called aphaeresis is used. Here the donor's blood is passed through a machine

which extracts the required component (e.g. plasma, platelets or red blood cells) and then returns the blood to the donor. Other collection decisions include the type of bag to be used. This decision is made at the moment of collection and has several impacts in the production process. Different types of bag sets can be used, from one single bag up to quadruple bag sets. The type of bag set to be used depends on what products are required to be produced from one unit. Fractionation processes use centrifugal forces to separate the different components, and this is done in different stages where each product is extracted in "satellite" bags. For instance, a triple set is used to obtain one unit of red blood cells and one unit of plasma, but a quadruple set can be used to obtain one unit of red blood cell, one unit of plasma and one unit of platelets, or one unit of red blood cells and one unit of cryoprecipitate.

Figure 2.2 depicts decisions and relationships in the collection stage. At the highest (strategic) level, decisions such as location, capacity definition, and staff definition reflect the long-term strategy of the organisation. These decisions are characterized by their importance and because they will affect other lower level decisions. Tactical level decisions are aimed at middle-term planning. At this level, decisions such as definition of policies, planning of collection campaigns and allocation of staff and collection points can be found. Finally, operational level refers to decisions that must be made daily or even in shorter time periods. This level comprises decisions such as scheduling, decisions on collection methods according to each donor and routes of collection. This classification presents a general idea, however depending on the specific blood supply chain decisions can be classified in a different way.

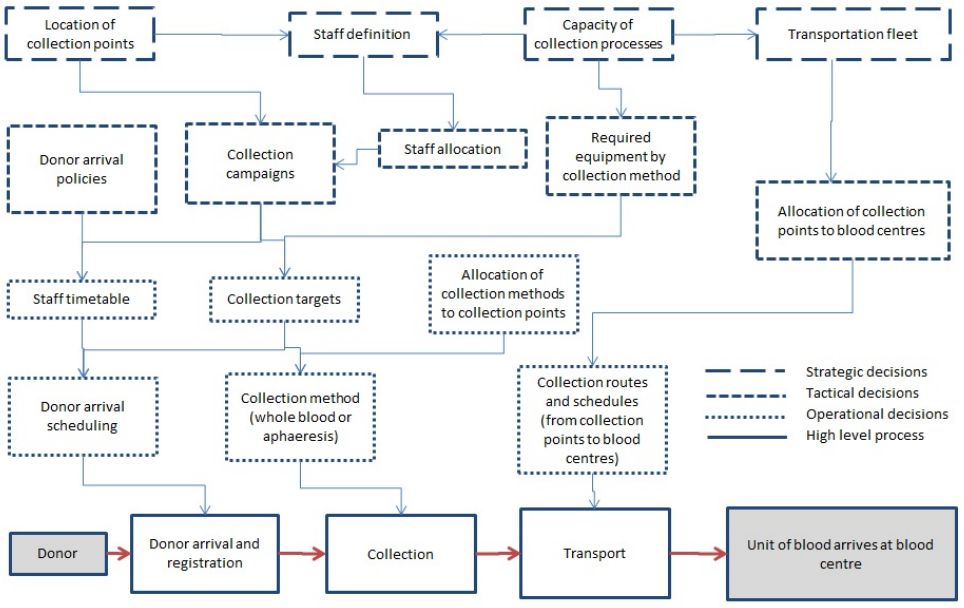


Figure 2.2: Decisions by hierarchy level in the collection stage.

Several different modelling approaches can be found to support decisions in the collection echelon. The problems studied include, for example, donor arrival estimation, planning for emergencies, donor motivation and behaviour, different collection strategies and capacity planning.

Prediction and classification of donor arrivals improve the collection process. One of the very earliest studies in the collection stage is presented by Cumming et al. (1976). A forecasting model is developed to improve blood collection plans and eliminate shortage and overstocking. The model includes transfusion and issuing sub-models, taking into account preferences in the use of the blood as well as differences in the use of the blood during a period of time of seven days. However this model has several aspects that make it less applicable in procurement situations, since the main issuing policy used is first-in-first-out (FIFO) and the weights or probabilities of use of the blood vary according to the time of the year. On the other hand, Melnyk et al. (1995) present a classification of donors based on survival analysis. This classification is used to track and measure all the activities in the collection process. The aim of this study is to improve the layout of the collection facilities and increase the satisfaction of donors, which is very important in encouraging people to donate regularly. This kind of approach could be

used to understand and study other aspects in the blood supply chain such as survival rates of blood units.

Additional blood is required in disasters and emergencies. Glynn et al. (2003) and Sonmezoglu et al. (2005) use log linear models, logistics regression and chi square tests to compare indicators such as volume and reaction rates during both normal and disaster periods. Both studies show that disasters considerably increase the volume of collections since these events have a major impact on the motivation of donors. However it is not always convenient to collect a large quantity of blood in a very short period of time. Moreover, risks are increased since adverse reaction rates for first-time donors are usually higher than for regular donors. Additionally, Boppana & Chalasani (2007) develop Markov chain models to determine the optimal acquisition rate of blood during emergencies. However, a debatable point about this article is that it assumes independence between shortage and outdate rates, whereas other studies such as Jennings (1973) and Sirelson & Brodheim (1991) show that these variables are related. An et al. (2011) present an evaluation of collection strategies in catastrophic scenarios. This paper evaluates situations such as in an epidemic, where the donor population decreases while at the same time demand increases. Finally, Jabbarzadeh et al. (2014) present a robust optimisation model to design a blood supply chain in case of emergency. The model support decisions such as location and number of permanent and temporary facilities, allocation of donors, quantity of blood to be collected and inventory. The model is solved using a robust optimisation methodology that considers scenarios designed by combination of critical parameters such as injury to death rate, hospital admission and blood transfusion rate.

The configuration of collection sites, the allocation of staff, and donor scheduling strategies have been also studied. Pratt & Grindon (1982) and Brennan et al. (1992) evaluate different configurations of collection points for different donor arrival rates. However, Brennan et al. (1992) extend this work, taking into account staff allocation and work rules. Both articles use simulation as an approach and measure the impact of changes in conditions using indicators such as the time taken in different stages in the collection process. Michaels et al. (1993) study strategies based on different ways of scheduling

donors. This study also proposes several scenarios about donors arriving late, inclusion of walk-in donors and batching donor arrivals.

Other studies in the collection stage concern factors that affect the motivation of donors. Godin et al. (2005, 2007) use regression to determine the relevance of variables such as intention, perception of control, anticipated regret, moral norm, age and past behaviour to understand motivation and determine key factors between first time and regular donors. Yu et al. (2007) present a similar study based in China, using several methodologies such as decision trees and k-medians. On the other hand, Custer et al. (2004) use Monte Carlo simulation and decision trees to evaluate different aspects of blood collection such as cost, collection and deferral policies. These models could help operations managers and decision makers improve collection, for instance, by improving the location of collection facilities and advertising strategies. Bosnes et al. (2005), Schreiber et al. (2005) and van Dongen et al. (2014) present studies aimed at studying the behavioural variables that affect donor arrivals, their commitment to future donations and the management of donors. Finally, a similar study is presented by James & Matthews (1996) who use survival analysis to study the key factors in donation cycles.

Other researchers have studied collection policies and collection methods and their impact on the performance indicators of the blood supply chain. Lowalekar & Ravichandran (2010) develop a simulation model to evaluate different collection policies. Those policies have been studied from an inventory theory perspective; however the same models can also inform collection decisions. Policies are studied with both fixed and variable quantities to be collected and varied times between donations. One of the main conclusions of this work is that it is not necessarily convenient to collect as much blood as possible. Alfonso et al. (2012, 2013) also develop a simulation model aimed at determining the capacity and staff required. The methodology firstly consists of a representation using Petri Nets to define the main events in the model. After this, the model is represented using discrete event simulation in order to include stochastic elements such as arrivals, processing times and donor behaviour. Two recent papers by Alfonso & Xie (2013) and Alfonso et al. (2014) present mathematical models for collection planning. The aim of the first model is to minimise products obtained from external suppliers.

This model considers important features such as the regional donation capacity, and optimises the quantity of blood to be collected each week. The second paper incorporates daily planning for the same self-sufficiency objective. Finally Madden et al. (2007) evaluate the impact of two different collection methods of red blood cells (RBC), using fractionation and double red blood cells donation by aphaeresis (2RBC): fractionation produces just one unit of RBC while 2RBC produces two units. This paper evaluates both methods under different policies such as European Travel Deferral, which is aimed at deferring donors who are ineligible to donate for various reasons, because of travelling and living in the UK and certain European countries during specific periods when Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt Jakob Disease (vCJD) were active.

Donor classification models have been also used to support decision making processes in the collection stage. The aim of classification is to identify important features of the donor population. For example, the proportion of men and women, the type of donor and age are all variables that should be taken into account in collection planning, since aspects such as donation cycles are different for men and women. Studying donor behaviour also provides important information about reasons for donation. Using such studies, researchers have identified critical variables in donor motivation, such as distance to the donation point and waiting times. Examples are presented by Lee & Cheng (2011) and Testik et al. (2012). In the first paper, the authors use data mining methodologies to classify donor behaviour. In the second paper, the authors use classification and queuing theory to determine staff requirements hour by hour. This is an important approximation to improve collection planning and support decision makers.

Ghandforoush & Sen (2010) develop a nonlinear integer programme to support the daily process of platelet production planning. The objective is minimising the costs of collection, production and shortages. Capacity constraints in collection and transport are included; however there are no inventory variables. The model does not consider a time index and the shortages are calculated using a historical rate. Optimisation models are also used by Gunpinar (2013). In one of the several models presented in his thesis, the author minimises the distance of collecting blood units from remote donors. This

model describes a problem rarely studied, and can serve as a basis to develop other collection strategies such as home collections.

Finally, other important features of the blood collection stage are also considered in some of these papers. Aphaeresis collection processes are considered in Custer et al. (2005), Madden et al. (2007), Bosnes et al. (2005), and Alfonso et al. (2012, 2013). The latter three papers also consider appointments in the collection stage. In addition, collection policies are studied in Lowalekar & Ravichandran (2010) , Alfonso et al. (2013) and Alfonso et al. (2014). On the other hand, ABO Rhesus groups in the collection stage are only considered by James & Matthews (1996). None of the models described in this section consider decisions about the types of bag to be used or payment for donation. These features, together with additional detailed information about the models such as the size of the problem and the type of study, can be found in Appendix A.

As we have seen, the literature on collection models is diverse; however there are still several areas which need further research. Examples of these are different collection alternatives, optimisation of cost, location of mobile collection centres and planning considerations such as periodicity in regular donors. All those aspects have not been addressed and represent opportunities to continue expanding knowledge in this area.

2.2.2 Production

Production is the stage where a unit of blood is received at the blood centre, and is then tested and possibly fractionated (broken down into components). This stage is concerned with replenishing inventories of blood products during normal and emergency periods. A large body of knowledge has been developed on inventories, however, the analysis is frequently focused on specific products and does not consider other products and sub-products generated during the fractionation processes. In this level, decisions are related to how to exploit the fractionation alternatives and advantages of collection methods to improve the performance of the blood supply chain.

Figure 2.3 is a schematic representation of the decisions in the production stage. Like for Figure 2.2, there is a hierarchical relationship among decisions. Strategic decisions in

production planning usually refer to determination of location and capacities, as these kinds of decisions are not easily reversible. Decisions such as staff allocation, production master plans, and facilities layout are classified as tactical and are affected by strategic decisions. Finally, operational decisions in production in the blood supply chain refer to daily planning such as scheduling of staff, paths for blood fractionation, timetabling and scheduling for testing. This is one of the most frequently studied levels in industrial supply chains; however, given the special features of blood these models are not easily applicable to the blood supply chain.

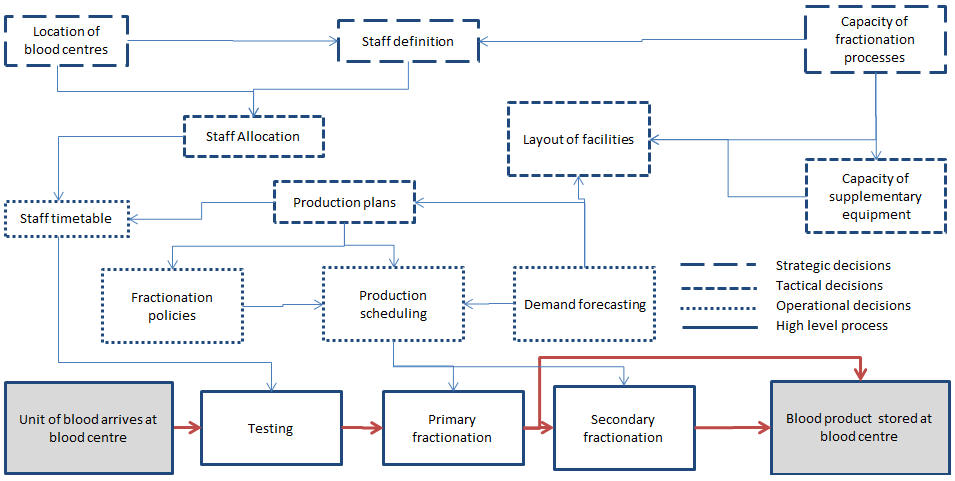


Figure 2.3: Decisions by hierarchy level in the production stage.

There are relatively few publications concerned with production decisions. However, in this section the literature concerned on blood products production is reviewed, including aspects such as production alternatives, single product production, platelet production, modelling approaches and models to study the impact of reducing shelf life.

Very few researchers consider several products simultaneously and the production alternatives to generate them. The first studies in production components are presented by Deuermeyer & Pierskalla (1978) and Deuermeyer (1979) who develop an analytical model to minimise the production costs of red blood cells (RBC) and platelets. In this paper, production decisions are associated with different production processes and are characterised according to the initial inventories of each product. This article introduces the idea of optimisation of production, since there are different alternatives to process a unit of blood. However the model is too simple to be relevant now, since current

fractionation processes includes alternatives with more than two products. In addition the model does not consider other features such as compatibilities and availability of donors.

In the case of a single product, production orders are derived directly from inventory levels. Sirelson & Brodheim (1991) develop a simulation model to support production decisions for platelets based on the inventory on hand. The authors develop profile graphs, where inventory levels are associated with accepted shortage and outdating rates. They also point out that inventory policies can be designed using only the mean demand as a single parameter, and that shortage and outdate rates are related mainly to the base stock. This model is interesting, but demand for platelets can vary over time and the inventory policies defined could become obsolete. Katz et al. (1983) propose a platelets production function. This equation is based on historical demand and deviations for each day as well as planned inventory and service level. This approach is similar to non-perishable inventory theory. Finally, Ledman & Groh (1984) develop production planning rules based on demand mean and variability and collection schemes. This report presents important concepts that have been less studied, such as different collection policies.

Given their short shelf life, platelets are regarded as highly perishable and several publications have dealt with the associated inventory problems. Haijema et al. (2007) develop a Markovian model to represent decisions on production and inventories of platelets. The model includes multiple periods as well as weekend breaks. Ordering, shortages and production are integrated in a general cost function to be optimised. This article considers two types of demand and different issuing policies to meet them as well as order-up-to policies. The first solution approach the authors tried was dynamic programming, but it was unsuccessful because of the problem size and number of states. Therefore, the problem was addressed using simulation and local search algorithms which gave near optimal solutions. Haijema et al. (2009) and van Dijk et al. (2009) present articles based on the same model. The first paper includes breaks such as Christmas, New Year and Easter. In the second paper, the model is used to introduce changes and study different scenarios. The scenarios studied by the authors consider differentiation of blood types

and changes in shelf life, as well as the crossmatch ratio and issuing policies. Uncertainty in demand and arrivals of donors are also considered. In the case of platelets the authors state that differentiation between ABO Rh groups can be ignored. This work is important since there is a real application which was implemented in Holland; in addition, the model is easily replicable. The heuristic presented gives a good approximation to the solution of this kind of problem; the problem's size and structure would normally make it intractable by exact methodologies.

Other studies have used different modelling approaches for production planning. For example Baesler et al. (2011) present a simulation model to study capacity and support decisions on capacity expansion. Most of papers in the literature assume infinite capacity in collection and processing and do not consider internal processes. However, Baesler et al. analyse the problem of resources used and internal waiting times and queues through simulation. Decisions about fractionation equipment and medical staff are made according to utilisation rates. This model could be extended to planning and scheduling collection campaigns based on capacity in order to avoid dissatisfaction of donors because of long waiting times. In addition, features such as fractionation alternatives, ABO Rh groups, special periods and different types of demand have been considered by some researchers. Fractionation alternatives are the least frequently studied. Of all the articles presented in this section, only Deuermeyer & Pierskalla (1978), Ledman & Groh (1984) and Baesler et al. (2011) considered this feature. In terms of type of products, the models presented in this section are mainly focused on platelets, with the exception of Deuermeyer & Pierskalla (1978) and Baesler et al. (2011) who also consider other products such as whole blood, red blood cells and plasma. On the other hand, ABO Rh groups are considered by Ledman & Groh (1984), Haijema et al. (2007), Haijema et al. (2009) and van Dijk et al. (2009). The latter three papers, and also Katz et al. (1983) and Sirelson & Brodheim (1991), also consider special periods such as weekends in their models. With exception of Deuermeyer & Pierskalla (1978) and Baesler et al. (2011) all these models include a periodical review inventory system. Finally, different types of demand are included in Haijema et al. (2007) and van Dijk et al. (2009). Further detailed information on additional features such as the size of the problem, horizon planning and type of data can be obtained in Appendix A.

2.2.3 Storage and Inventory

Inventory is the stage of the blood supply chain that has received the most attention in the literature. From 1960 onwards, researchers began to develop new methodologies to study inventory policies for blood products. The perishable nature of blood products, together with special features such as crossmatching and mismatching, considerably increases the complexity of this problem, and has stimulated many theoretical developments in this area which have had wide applicability beyond the blood supply chain.

Figure 2.4 shows the relationship between decisions on inventory. The figure is general, however the complexity of platelets inventory can be greater than that of other blood products since the shelf life is much shorter. Decisions in this echelon have been mainly related with definition of inventory policies; however, some of the models presented in the literature are focussed on specific decisions and do not consider constraints and features such as availability of donors, proportionalities and compatibilities that could affect decisions at this stage.

Decisions in this stage can also be classified according to hierarchical levels. Again, long term planning is associated with strategic decisions such as network design. In addition to location decisions, this stage also covers decisions such as information systems, which play a very important role in inventory management. Tactical decisions in this stage refer to inventory policies definition and staff allocation. Mismatching and crossmatching policies can be also defined in this level, although these policies can be altered in emergency situations where they become more operational decisions. In the lowest level decisions are related to daily quantities to order, how to meet special orders and what specific products should be issued in order to fulfil demand.

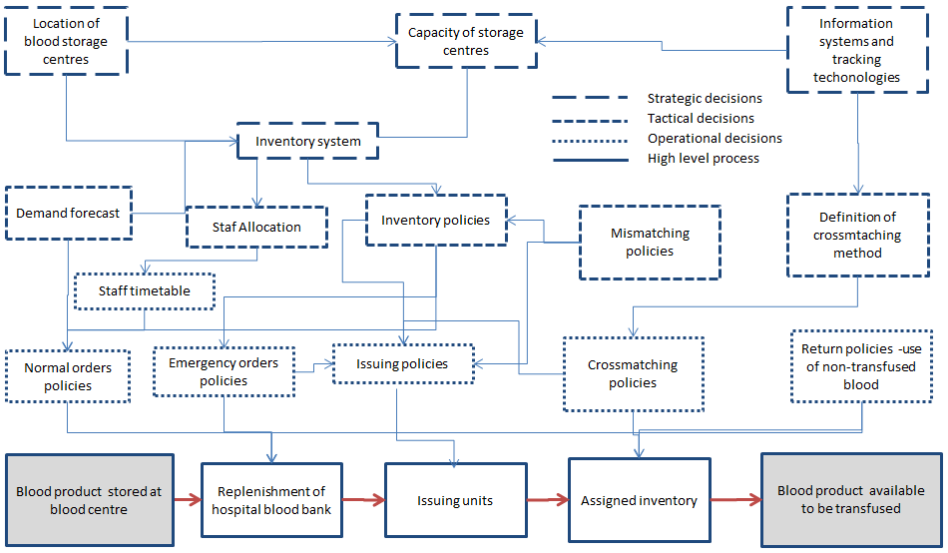


Figure 2.4: Decisions by hierarchy level in the inventory stage.

Methodologies such as analytical models, statistical approaches, Markov chains, queuing theory, optimisation, simulation, and combinations thereof have been proposed to address this problem. However, even now there is no practical theory to calculate optimal policies for some blood products.

One of the earliest approaches to the study of blood inventory problems was analytical modelling. Two analytical models to evaluate different aspects of blood inventory management are presented in Cohen (1976) and Nahmias & Pierskalla (1976). Cohen's paper is aimed at finding optimal ordering policies for any perishable product, taking blood as an example. This model considers important features such as perishability and backlogging, however results are presented just for three periods and the current shelf life of RBC is 42 days. Even platelets have a longer shelf life period than 5 days. Nahmias & Pierskalla (1976) present a model considering two types of demand and two different policies to meet demand. Pierskalla & Roach (1972) evaluate first-in-first-out (FIFO) and last-in-first-out (LIFO) policies, finding that, in most of the scenarios evaluated, FIFO outperforms LIFO, according to key performance indicators such as shortage, outdate, assigned inventory and cost. Finally, other examples of analytical models can be found in Chazan & Gal (1977) who find bounds for the expected outdating rates; Jagannathan & Sen (1991) who study the impact on shortage and outdate

rates of changes in crossmatching parameters; and Pegels et al. (1977) who use a single blood centre model to evaluate different strategies such as using frozen red blood cells and improving inventory control and donor scheduling.

Other articles also present analytical procedures to determine inventory and ordering rules. This approach is aimed at finding functions and profiles to support the decision-making process. Sapountzis (1985) develops characteristic curves to determine outdating probabilities for each RBC type in hospitals. Omosigho (2002) presents a general formula for calculating the probability of use for perishable products. According to Omosigho (2002), in the specific case of the blood supply chain this probability can be assumed to be the crossmatching ratio. Telles et al. (2013) present a typical inventory model for blood products. However blood is treated as a normal product since special features are not considered. Blake et al. (2010) discuss the convenience of using cost as objective for platelets inventory policies. In this work the authors also present a simplified methodology for ordering platelets, based on service levels. This methodology was applied to different sized hospitals, finding that it works better in hospitals with more stable demand. Finally, Zhou, Qu, Li, Zhao, Suganthan & Zhang (2011) present an analytical model to define optimal inventory policies for platelets. The model extends analytical policies to three periods and also includes different replenishment modes, such as normal and optional.

Markov chains and statistical approaches have been widely used for many years to study the performance of blood inventory systems. Pegels & Jelmert (1970) use a Markov chain model to assess two different issuing policies and calculate its impact on blood inventory. However, this model is criticised by Jennings (1973) who argue that the model is not clear about transition probabilities and even that it is not a Markov chain model. On the other hand, Brodheim et al. (1975) use a Markov chain model to represent the behaviour of an inventory system and distribution policies. The model assumes stationary demand and is aimed at calculating shortage and outdating rates as well as bounds and inventory parameters. This approach is also used by Mole (1975) to generate profile curves of shortage/demand versus wastage/replenishment for two different demand distributions. Statistical methods are used by Frankfurter et al. (1974) to try to predict the behaviour

of inventory based on the main variables of the system. Similar methods are proposed by Critchfield et al. (1985) who use time series forecasting methodologies such as moving average, Winter's methods and exponential smoothing to predict the use of platelets concentrates in a blood centre. The results were less accurate than empirical prediction, but the authors highlight that reductions in outdates were obtained using the method. Finally, Silva et al. (2013) propose seasonal ARIMA models (SARIMA) to forecast demand of blood products as well as arrivals of donors. The paper specifies an automatic procedure to be applied without human intervention.

Queuing theory has also been applied, modelling blood collection as arrivals and demand as a service. Some models include transient features such as impatient donors who are not prepared to wait more than a given time. Goh et al. (1993) develop a queuing model to evaluate two policies, unrestricted and restricted ways of meeting demand, in an inventory system with two stages. The unrestricted policy allows fresh blood to be used to meet demand for either fresh or old blood, whereas the restricted policy does not allow fresh blood to be used to meet demand for old blood. Moreover, Kopach et al. (2008) present an elaborate queuing model that considers various costs in addition to shortage and outdate rates. The model also considers two types of demand and several strategies to meet each type. However, such models often include strong assumptions that can make them less applicable in practice. For example, assumptions about the distribution of donor arrivals and demand over time can affect the results, since donor arrivals can be affected by policies such as the maximum quantity collected, and demand can also vary over the time period. In addition, these models do not include the crossmatching ratio and the crossmatching period, which are very important features in the real world setting.

Given the complexities of the system, simulation has been one of the most important approaches to modelling the blood inventories. One of the earliest simulation models was presented by Elston & Pickrel (1963) who use Monte Carlo simulation to evaluate scenarios for blood inventory management. This work showed that indicators such as the inventory level, the expiration percentage, the age of the blood and shortages, could be improved. This approach is also used by Cohen & Pierskalla (1975) and Vrat & Khan

(1976), to evaluate different aspects on blood inventory. In Cohen & Pierskalla (1975) the methodology is used to evaluate issuing and crossmatch period policies. The crossmatch release period is the length of time a unit of blood is stored in assigned inventory before it is returned back to unassigned inventory, normally because the patient is deemed to be in no further need of it. The metrics to evaluate the different scenarios are units transfused, shortages, outdates, cost, and assigned and unassigned inventory. The model presented by Vrat & Khan (1976) has similar metrics but in this case crossmatching features are not considered. Brodheim et al. (1976) develop profile curves to define inventory levels based on shortages and mean demand. The proposed curves are a simple and effective way to support blood bank managers. The use of substitute products has been studied in Cumming et al. (1977). Using simulation, the authors evaluate the use of frozen red blood cells in avoiding shortages; however this practice is not common at this time. A similar study was published by Friedman et al. (1982), who study the impact of both reducing non-type O inventory to exploit the compatibilities of this blood type and also an extension of the shelf life from 21 to 35 days. Currently it is widely accepted that shelf life of RBC is 42 days, but recent evidence suggests it is preferable use "young" blood. Recent studies such as Fontaine et al. (2010) and Blake et al. (2013) have evaluated the impact of reducing the actual maximum shelf life of RBC in blood bank indicators. Pereira (2005) uses Monte Carlo simulation to evaluate an alternative to crossmatching called Type and Screen (T&S), which does not assign inventory to patients. According to this paper, T&S outperforms crossmatching on all the key performance indicators. However, to date T&S has still not been completely accepted by medical staff, despite some successful cases as presented by Georgsen & Kristensen (1998). Finally, Kamp et al. (2010) present a System Dynamics (SD) model to evaluate strategies under critical scenarios such as pandemics, when demand increases but the donor population decreases. However, SD has been less used than other techniques to study the blood supply chain.

Optimisation has rarely been used in blood inventory. Given the complexities of this kind of problem the use of optimisation seems to be impractical. The size of the problems and the nature of the variables can affect the quality of solutions obtained. However, this also depends on the specific application. A goal programming model is proposed by Kendall (1980) to allocate blood units to hospitals considering the remaining shelf life.

The criteria to evaluate the solutions in this model are availability stock levels, fresh blood availability, age of blood, rate of outdating, and cost. Recently, Gunpinar (2013) and Gunpinar & Centeno (2015) presents optimisation models aimed at minimising total cost (purchase cost, holding cost, wastage cost, outdate cost, and outdating cost). The models seek to generate an inventory plan considering internal parameters such as capacity and lead time. Finally, other articles such as Britten & Geurtze (1979), Erickson et al. (2008) give results of application of decision rules, however, not much information is given about the methodologies used to define the parameters.

When two or more methodologies are combined, models can be more robust and different features can also be included. Statistical methods, economic modelling, simulation and inventory theory are combined by Cohen & Pierskalla (1979) to calculate a single equation to define optimal inventory policies. The aim of the model is to support the decision-making process of blood bank managers. Cohen et al. (1983) use the same model to estimate the impact of extending the shelf life from 21 to 35 days. Recently, Li & Liao (2012) develop a model using the Taguchi method, combined with neural networks and genetic algorithms, to estimate optimal parameters in a blood supply chain. This methodology enables optimal minimum and maximum inventories to be found, as well as optimal donor arrival rates. This approach seems to be promising, since it can evaluate many different configurations in reasonable times. However the model did not include important features such as crossmatching. Duan & Liao (2013) apply Sample Average Approximation to include uncertainty in an optimisation model aimed at minimising the expected outdate ratio. The model also considered maximum shortage constraints as well as centralised and decentralised inventories. Duan & Liao (2014) combine discrete event simulation and heuristic methodologies to generate an inventory plan, considering compatibilities and reduction of the shelf life of blood products. Finally, a recent publication developed by Blake & Hardy (2014) presents a simulation framework to evaluate inventory policies in both supplier and customer. Using response surfaces generated by simulation the methodology fits regressions to establish equations that can represent the surfaces. The equations are combined in a weighted non-linear function that is finally optimised to generate changes for inventory policies that satisfy objectives such as outdating, shortages and the numbers of normal and emergency orders.

Most of the models presented in this section concern whole blood or red blood cells inventories. However, papers such as Critchfield et al. (1985), Blake et al. (2010), Zhou, Qu, Li, Zhao, Suganthan & Zhang (2011), Duan & Liao (2013) focus on platelets inventories while other papers such as Gunpinar (2013), Silva et al. (2013) and Telles et al. (2013) consider multiple products in the models. ABO Rh groups are explicitly considered in articles such as Elston & Pickrel (1963), Jennings (1968), Frankfurter et al. (1974), Vrat & Khan (1976), Brodheim et al. (1976), Fontaine et al. (2010), Duan & Liao (2013) and Blake & Hardy (2014). In terms of inventory strategies, most models include typical periodical and continuous review policies. However other authors such as Blake et al. (2010) and Blake & Hardy (2014) present a more elaborate policy combining periodical and continuous review systems. Other policies based on expected outdates and the age of the blood products are presented in Duan & Liao (2013, 2014). With the exception of a few publications at the early stages of research on inventory policies, the articles use FIFO (first in first out) as the issuing policy. On the other hand, emergency orders are included in some models, such as Kendall (1980), Erickson et al. (2008), Kamp et al. (2010), Zhou, Qu, Li, Zhao, Suganthan & Zhang (2011) and Blake & Hardy (2014). Finally, other features such as the crossmatch ratio and crossmatch release period were included and studied in the 1980's and 1990's, for example Cohen & Pierskalla (1979), Britten & Geurtze (1979) and Jagannathan & Sen (1991). However, policies such as Type & Screen avoid the complications for inventory planning generated by these features. Further information on the features presented here can be also found in Appendix A, together with information about the models such as problem size, type of information and type of study.

2.2.4 Distribution

Collection, production and inventory are all independent of the configuration of demand points in the blood supply chain. However distribution processes can vary considerably: in places where there is a regional blood service, blood can be transported from one blood centre to another if there is a shortage in one location and an over-supply in another. Moreover, distribution also includes the internal transfer of blood products

from a hospital blood bank to the point of care. Generally, hospitals provide daily requests for blood from their local blood centre, based on historical data, forecasts and clinical knowledge. There are published tables specifying how much blood is typically required for each type of major surgery. In most countries, emergency requests can also be placed and additional supplies are then "blue-lighted" using a fast vehicle, e.g. if there is a major incident. The goal is to deliver the correct quantity of the correct product to the patient at the moment it is required.

Figure 2.5 presents a general schematic representation of distribution decisions. Distribution decisions can be found throughout the supply chain: even the collection stage includes decisions about how to pick and distribute whole blood to the blood centres. The framework presented in Figure 2.5 corresponds mainly to the process of transporting "finished" product from inventories in blood centres to hospitals to be transfused to patients. However, models and methodologies can be extended to other areas that contain distribution decisions. Long term decisions in the distribution stage relate to the strategy for product delivery: choice of types of vehicles, capacity and staff. These decisions will affect tactical decisions such as routing and allocation. Planning in the short term implies scheduling of vehicles, packing, transhipments between different points and meeting time window constraints. The distribution stage in the blood supply chain must handle complex situations, since in some cases it is not desirable to maintain inventory in low demand hospitals for scarce products such as AB-negative RBC. The inventory must be kept in blood centres and will only be dispatched to hospitals in emergencies, at very short notice.

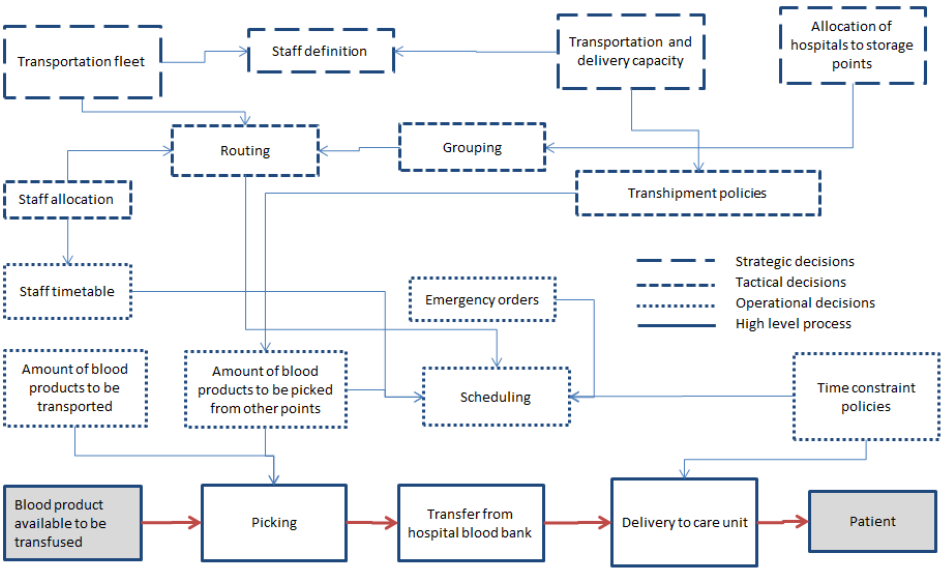


Figure 2.5: Decisions by hierarchy level in the distribution stage.

The analysis of the literature for this aspect includes location decisions as well as allocation and distribution strategies. Papers that cover different aspects such as crossmatching strategies, blood products allocation, facility location and delivery strategies are analysed and presented, highlighting the contributions and important aspects.

Blood is a raw material produced by donation from human beings. In many countries donation is voluntary and donors need to be assured that their blood is used to good purpose. Collecting blood requires an enormous effort, which means that its spoilage and wastage need to be reduced as much as possible. Yahnke et al. (1972, 1973) study the effect of returning unused blood from the hospital to the blood centre, and find that this practice can decrease the outdate rate; it should be noted that today this practice is not allowed in most developed countries. The authors also propose a different indicator aimed at measuring the impact on each hospital. This indicator is called the effective outdate rate and its objective is to avoid returns of very old blood. Dumas & Rabinowitz (1977) propose two policies to reduce the outdating rate. The first policy uses double crossmatching to increase the probability of use and reduce the outdate rate. Under this policy, each unit is assigned to two different patients and each patient is assigned two different blood units. Unfortunately, this policy was not well received by physicians. However, the other proposed policy is widely used now and is focused on the

use of substitute products (mismatching). Provided the compatibility criteria are met, demand can be satisfied by the use of more common products. Nowadays, there are even preferences in the use of each substitute product. Finally, Sapountzis (1984, 1989) develops optimisation models to reduce outdating rates based on the activity level of each hospital and inventory allocation under both deterministic and stochastic demand.

Allocation strategies are also aimed at decreasing wastage and shortages. Prastacos (1978), Brodheim & Prastacos (1979) and Prastacos & Brodheim (1980) develop models to reallocate the blood inventory of several hospitals in a region at the end of each planning period. In the first paper, analytical methods were used to calculate optimal values of two different strategies, rotation and retention. The objective optimised is the sum of the shortage and wastage costs. The second paper is similar, but in this case the author uses mathematical programming to determine the policies which minimise the use of fresh blood. Furthermore, Prastacos & Brodheim (1980) develop a model to minimise the transhipments considering pre-schedule deliveries, a fixed quantity of old blood returns and rotation and retention policies according to the age of the blood. Finally, a formalisation of the models developed is presented in Prastacos (1981). In this paper the myopic policies presented in previous articles are compared with optimal policies, permitting the generation of bounds to measure the goodness of the myopic strategy. The authors found that there is not much difference from optimal policies. The main reason to develop myopic policies is that these are easier to implement in practice than the optimal inventory policies presented in other publications.

Location decisions are typically considered as strategic in any supply chain. In the blood supply chain these kinds of decisions are also very important, since the distance between donors, blood centres, and demand points can play an important role in the improvement of different indicators in the blood supply chain. Or & Pierskalla (1979) present an integrated mathematical model to locate blood centres and allocate hospitals to them, which aims to minimise the distance travelled. The paper also contains two algorithms to solve this model. The objective function is only concerned with distance: costs are not considered. Another contribution in location models is presented by Jacobs et al. (1996) who developed an integer linear programming model to evaluate

location alternatives and decisions such as allocation of donors to collection points, allocation of collection points to blood centres and quantities of blood to be collected. The model's main objective is the minimisation of distance, meeting assignation, capacity and demand constraints. Sahin et al. (2007) present two models to support decisions on location and allocation in Turkey. The first model minimises the weighted distance between demand points and blood centres. The second case minimises the number of blood stations considering distance covering constraints. The models are modifications of the well-known pq-median and set covering models and both were solved using optimisation software without any additional solution methodology. Other articles also aimed at locating facilities are presented by Cerveny (1980), Price & Turcotte (1986) and more recently Çetin & Sarul (2009). These articles present heuristics and combined methodologies to determine the location of a facility. The main objective is to minimise distance; however, in Price & Turcotte (1986) other criteria such as accessibility and space availability are also considered.

Routing-scheduling models and vendor managed inventory (VMI) have been applied to reduce shortages and distance indicators in the distribution stage. Federgruen et al. (1986) present two models for allocation and routing inventory problem aimed at minimizing shortage cost, transport cost and outdate cost. Sivakumar et al. (2008) develop a mixed methodology combining the Vehicle Routing Problem and the Analytic Hierarchy Process to study an allocation-routing problem in a blood supply chain in India. Recently, Hemmelmayr et al. (2009) presented a model to improve the assignment of hospitals to the routes planned by a blood bank. The model is based on VMI methodologies which imply that hospitals do not define the quantities and delivery dates, but instead the blood bank will program the deliveries based on stationary deterministic demand. Since demand is deterministic shortages are not considered. The model aims to minimise the distance travelled and considers time constraints.

Finally, some models include emergency ("blue light") orders. Gregor et al. (1982) study distinct distribution strategies such as changing the number of vehicles and redefining inventory levels to minimise several objectives including the reduction of emergency orders. Hemmelmayr et al. (2010) present an improved version of their previous model.

In this case, demand is considered as stochastic and the model includes several forms to meet demand in case of emergencies. The solution methodology proposed is a combination of Sample Average Approximation and metaheuristics. The methodology proposed is robust and can be used to address other problems in the blood supply chain. Banthao & Jittarnai (2012) develop a mathematical model to locate blood banks using distance coverage policies. This model is similar to presented by Çetin & Sarul (2009) but in this case the objective is minimisation of the total cost: normal ordering cost plus emergency ordering cost. As a final point, few of these models consider the possibilities of meeting demand using substitute products, which can be a practical alternative in case of shortages and emergencies.

Other important features such as the use of substitute products, returns and transhipments are included in some of the papers presented in this section. The use of substitute products is studied in Dumas & Rabinowitz (1977) while returns are allowed for example in Yahnke et al. (1973), Dumas & Rabinowitz (1977), Prastacos (1978), Prastacos & Brodheim (1980), Gregor et al. (1982) and Federgruen et al. (1986). Transhipments or interchange of blood products is considered in the models presented by Yahnke et al. (1973), Prastacos & Brodheim (1980), Sahin et al. (2007) and Sivakumar et al. (2008). Finally, some distribution models such as Hemmelmayr et al. (2010), Sapountzis (1984, 1989) and Gregor et al. (1982) also consider blood types in the distribution strategy. A complete presentation of the features mentioned for each article of this section, together with additional information such as problem size, type of data and type of products considered, is available in Appendix A.

2.2.5 Integrated Models

Features of the blood supply chain such as perishability, blood types and uncertainty of supply and demand affect decisions at all echelons of the blood supply chain. These features add complexity to the decision making process and differentiate the blood supply chain from other supply chains, and from other perishable products. Figure 2.6 presents a general schematic of the features and their relationships with each echelon of the blood supply chain. This Figure also presents the main performance indicators of the blood

supply chain such as outdating rate, shortage rate and cost. A less frequently studied indicator is the number of donors required to meet demand. Since demand for blood products is increasing and the donor population is decreasing, this indicator may play an important role in blood bank management. Figure 2.6 relates the main features of the blood supply chain and the indicators and stages directly impacted by each feature. This Figure also illustrates the complexity of the blood supply chain and shows why it is different from industrial supply chains.

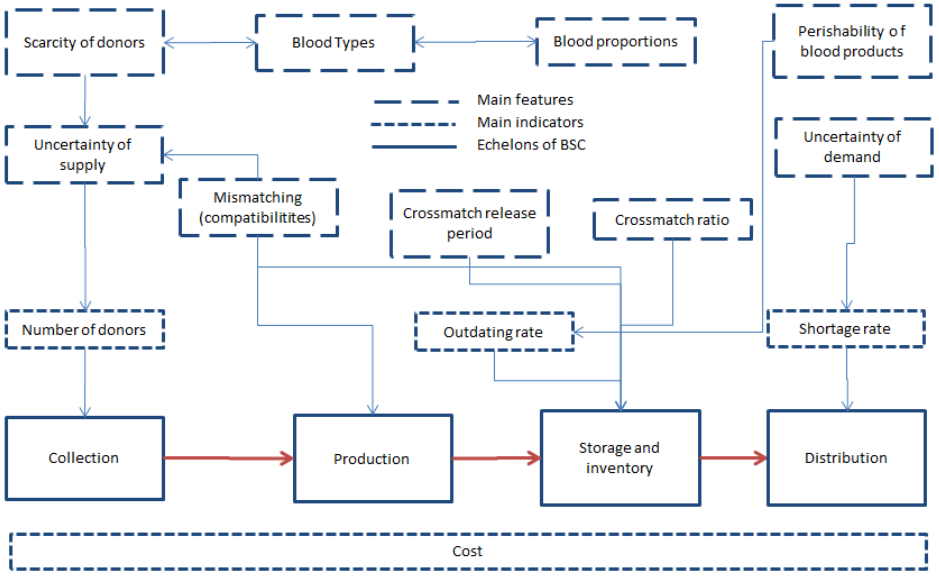


Figure 2.6: Representation of relationships between main features and echelons in the blood supply chain.

The majority of the literature in the blood supply chain is focused on individual echelons and does not consider relationships between the different stages. For example, models for collection often do not consider production and distribution policies. Models for inventory management very often assume that there are no limitations on the number of units that can be collected. However, recent publications on the blood supply chain often aim to connect donors with patients, considering flows of blood and blood products throughout the supply chain. Different methodologies have been used, such as simulation, optimisation and hybrid approaches to study and improve the blood supply chain.

One of the main methodologies to represent and study the blood supply chain is discrete event simulation (DES). Page (1980*a*) presents one of the first articles using DES to study

the blood supply chain, evaluating distinct strategies such as heuristic procedures for inventory allocation, forecasting of inventory levels and recycling of old blood to reduce the cost per unit transfused. Rytilä & Spens (2006) develop a DES model to study inventories and distribution policies measured through indicators such as outdating, cost and back orders. This model also includes different aspects of the supply chain such as compatibilities, integration between hospitals and blood centres, and the crossmatch release period. Although the authors mention the optimisation of inventory policies, they do not provide much information about what methodology they used. An important point in this article is that it was developed in conjunction with medical staff, who helped to implement several proposals derived from the model. Katsaliaki & Brailsford (2007) use DES to provide a complete representation of the blood supply chain, including collection, production, inventory and distribution stages. This DES model is based on the National Blood Service in the UK, specifically on the processes developed in typical hospitals in Southampton. Changes in policies are proposed to improve the supply chain, mainly based on inventory and distribution stages, with other echelons represented to study the flow of the blood along the complete supply chain. A similar study is presented in Yegül (2007); in this paper the author develops a more generic model considering collection points, blood centres and hospitals. The model developed allows transhipments and incorporates heuristic mismatching rules. This work is aimed at evaluating different scenarios of the structure of the blood supply chain in Turkey. Finally, Baesler et al. (2014) also present an integrated DES model. This paper is aimed at developing inventory policies considering emergency collection campaigns. Reorder points are estimated to minimise wastage and outdating rates, with a decision rule to start an extra collection campaign. The model considers several stages of the blood supply chain, but is mainly focused on collection stage.

Another simulation paradigm used to study the blood supply chain is Monte Carlo simulation. Lowalekar & Ravichandran (2011) and Simonetti et al. (2014) present studies based on this methodology to support decisions. In the first paper, the authors model the collection and production stages. In collection, different strategies are studied, including fixed and variable collection quantities. In the production stages, the authors evaluate different fractionation rates and develop profile curves to help the decision maker to

define policies. Their model includes several blood products, however collection methods such as apheresis are not considered since these methods are not common in India. The second paper combines DES and Monte Carlo simulation to study different issuing policies, evaluating availability and shortage indicators. The results show that FIFO, newest and oldest policies differ considerably on the availability of units. However other indicators such as outdating are not significantly different. On the other hand, the model includes a new idea about mismatching policies, creating a decision rule for preferences in the use of substitute products. Finally, the models consider a decision rule to mismatch blood products. This process consists of a table of preferences in the use of substitute products; these preferences are often used in blood banks, but it is the first time that they have been explicitly included in a model.

Mathematical programming and data mining combined with geographical information systems (GIS)-based analytics are used by Nagurney & Masoumi (2012) and Delen et al. (2011) respectively to model the blood supply chain. The model developed by Nagurney & Masoumi (2012) is claimed to be the first attempt to use mathematical programming to optimise the whole blood supply chain. This model considers the blood supply chain as a network problem, defining different nodes, arcs and flows to represent the entities and relationships of this supply chain. The article also includes algorithms to generate optimal flows throughout the whole supply chain as well as optimal results of basic instances. An extension of this work is presented in Nagurney & Masoumi (2012). The main differences are the inclusion of discarding cost along the supply chain and the consideration of the arc capacities as decision variables. However, both articles are focused on a strategic perspective and do not consider important features of the blood supply chain such as the crossmatching period, compatibilities and multiple products. Finally, Delen et al. (2011) present an application of several methodologies such as data mining, GIS-based analytics and optimisation to improve the blood supply chain in the armed forces. This application is interesting since the blood demand and the blood supply chain in the armed forces have several differences from a typical blood supply chain, such as emergencies arising from combat, resource limitations and geographical constraints. However the article is focused on the software developed and does not describe

in depth the models and methodologies used. Finally, Abdulwahab & Wahab (2014) propose a combination of methodologies such as news vendor problem, linear programming and approximation dynamic programming to address the platelets inventory problem. The paper highlights that there is no need to resize the problem, as previous studies have described. Another important contribution is the inclusion of blood types and use of substitute products.

Multi-objective approaches and simulation optimisation methodologies have also served to evaluate different aspects. Firstly, Kendall (1980) use multi-criteria methods to find the best configuration of blood supply chain planning. Using predefined options, the article develops a trade-off methodology to find the best combination of policies in different aspects such as collection, budget, acceptable shortages and outdates, and inventory levels.Currently, there are more robust multi-objective methodologies; however few articles consider more than one objective. Finally, Lang (2010) uses a combination of simulation and heuristic methodologies to evaluate the impact of both transhipment and substitution. Both concepts are very important to the goal of reducing outdating and shortage rates since they present alternatives to supply demand. Although these concepts are not new, very few models consider these aspects.

In addition, some papers present discussion on important features of the blood supply chain such as .Considerations about the duration of shelf life of RBC and its impact. Recently, Blake et al. (2013) published an article which studied the impact of reducing the shelf life in three scenarios: 28, 21 and 14 days. In the 1970's, research on transfusion was aimed at extending the shelf life, and the result of this is that currently the shelf life of RBC is usually 42 days. However as Blake states "there is a body of literature that suggests poorer clinical outcomes when older RBCs are used." (Blake et al. 2013). Under this premise, Blake et al. developed a simulation model to evaluate shorter RBC shelf life, taking into account inventory, outdating, shortage and emergency indicators. This kind of model could be useful to measure the impact of the use of substitute products, since there have not been studies specifically designed to measure the impact of this important feature of the system. Papers discussed in previous stages such as Fontaine

et al. (2010) and Duan & Liao (2014) also consider reductions in the shelf life of the RBC.

Integrated models are aimed at studying more than one stage in the blood supply chain. However it is almost impossible to represent every single feature of each echelon in one single model. Some features such as blood type are independent of the echelon analysed. Most of the models presented in this section, with the exception of Kendall (1980), Delen et al. (2011), Nagurney & Masoumi (2012) and Nagurney et al. (2012), consider blood types as a feature in the models developed. One of the less frequently studied features is fractionation. Of all the articles presented in this section, only Lowalekar & Ravichandran (2011) and Baesler et al. (2014) considered fractionation. On the other hand, many of the models described in this section include the collection stage. Kendall (1980) and Lowalekar & Ravichandran (2011) considered collection goals and policies while Baesler et al. (2014), Blake et al. (2013) and Abdulwahab & Wahab (2014) represent collection amounts as stochastic parameters associated with probability distributions or expected values. The latter three papers, together with Kendall (1980), Katsaliaki & Brailsford (2007), Yegül (2007), and Lang (2010), considered inventory policies explicitly in the models presented. Distribution features such as issuing policies, mismatching policies, crossmatch rate and crossmatch period are included in some models discussed in this section, with the exception of Baesler et al. (2014) and Lowalekar & Ravichandran (2011) who mainly focus on the initial stages of the blood supply chain and do not consider distribution aspects. Finally, transhipments and interchange of products are included in the models presented by Page (1980*a*), Rytilä & Spens (2006), Yegül (2007), Lang (2010), Delen et al. (2011) and Blake et al. (2013). Additional information about each model presented in this section can be found in Appendix A.

2.3 Conclusions

The blood supply chain remains a very active research area. There is renewed interest in research in this field, judging by the number of recent publications. In this review we present a structured taxonomy of the state of the art of quantitative models as well as

a decision making framework in the blood supply chain. In this final section we shall discuss aspects such as less frequently studied decisions, modelling needs, modelling approaches, and potential future changes in the blood supply chain.

We have already identified that in each echelon there are some decisions which have been rarely studied to date. In the collection stage, the literature has mainly focused on donor behaviour and the location and configuration of blood collection points. However we found very little discussion on the allocation of donors to different collection methods. We found no models studying the relationship between efficiency and the cost of different collection methods. Production is perhaps the least well explored stage of the blood supply chain. There is a considerable body of literature on inventory control, but very few articles that consider the process of fractionation, where blood products are derived from whole blood as a result of separation processes that generate at least two products. This means that it is not necessarily efficient to manage inventories of different blood products independently. The majority of the literature concerns the inventory stage. Recently inventory research has focused on platelet concentrates. However the question of centralised or decentralised inventory has been rarely studied, and more research into the best use of substitute products is required. Finally, we found widespread application of location and allocation methods in the distribution stage. However problems such as product allocation to production centres, blood transhipments, substitute products and collaborative schemes need more attention.

We found very few examples of integrated models and inclusion of multiple features. Most of the literature focuses on one single echelon. This can lead to a myopic view of the blood supply chain. Collection methods and goals are not governed by production policies. Inventory policies often does not consider the supply constraints. Production does not consider the age of the inventory. Those are all examples of problems by considering echelons individually. On the other hand, features such as the crossmatching rate and release period, mismatching, and multi-products are not typically considered at the same time, leading in some cases to unrealistic and impracticable solutions. We argue that there is a clear need for modelling the entire process flow in the blood supply

chain. This can help to identify bottlenecks as well as evaluate policies from a whole-system perspective. At the very least, integrated models would recognise the existence of contraints in the preceding and succeeding echelons. Of course, such models are challenging to develop and call for the use of mixed methodologies.

Recent publications tend to use more than one methodology to address blood supply chain problems. In the early years, analytical procedures and Markov chains were commonly used for inventory control problems, whereas statistical methods were used to study donor behaviour and forecast demand. However, the complexity inherent in each stage of the blood supply chain means that it is often necessary to combine methodologies. One popular combination is simulation plus optimisation. Using these approaches in combination enhances the possibilities of making practical improvements to the system. Both methodologies have advantages and disadvantages, but these are largely complementary and by using them jointly, robust decision models can be created. This interaction of techniques can be achieved in different ways. The combination of Monte Carlo simulation with optimisation is a technique often used in stochastic optimisation. On the other hand, the optimisation of simulation parameters is also used. In the case of the blood supply chain this combination can be an interesting hybrid methodology to generate efficient solutions. Simulation can be used to represent, in a realistic way, the system features and flows of donors, blood, blood products and information throughout the whole supply chain. Moreover, optimisation can be used to define the parameters of the whole supply chain such as collection and production policies.

Recent scientific developments such as Type & Screen and the proposed shorter shelf life of red blood cells will also create a need for new research. Changes in the features of the blood supply chain can affect performance both positively and negatively. Type & Screen provides a very efficient alternative to crossmatching since there is no physical assigned inventory. Crossmatching is one of the features of the blood supply chain that contributes to increased outdating rates, since it leads to unrealistic inventory levels. On the other hand, studies such as Blake et al. (2013) consider the impact of reducing the shelf life of blood products, which in the case of red blood cells may to lead to improved clinical outcomes. This change could greatly affect the performance of the blood supply

chain, since RBC is the main blood component in terms of demand. Those changes as well as other changes such as deferral policies and mismatching preferences impact the blood supply chain in different ways. It is clear that this field will continue to be a fertile area for research for many years, leading not only to improvements to patient outcomes in the real world, but also contributing to methodological developments in modelling.

Chapter 3

Simulation-Optimization Model for Production Planning in the Blood Supply Chain

Abstract

Production planning in the blood supply chain is a challenging task. Many complex factors such as uncertain supply and demand, blood group proportions, shelf life constraints and different collection and production methods have to be taken into account, and thus advanced methodologies are required for decision making. This paper presents an integrated simulation-optimization model to support both strategic and operational decisions in production planning. Discrete-event simulation is used to represent the flows through the supply chain, incorporating collection, production, storing and distribution. On the other hand, an integer linear optimization model running over a rolling planning horizon is used to support daily decisions, such as the required number of donors, collection methods and production planning. This approach is evaluated using real data from a blood center in Colombia. The results show that, using the proposed model, key indicators such as shortages, outdated units, donors required and cost are improved.

3.1 Introduction

The blood supply chain involves the collection, production, storing and distribution of blood and its components. Special features make the blood supply chain different from typical industrial supply chains and render it a very challenging study area. In many countries, blood is considered a highly scarce resource since only a small percentage of the eligible population actually donates blood. In the US this percentage is about 10%; however, in medium- and low-income countries this rate is much lower WHO (2014). A recent review by Osorio et al. (2015) includes 110 papers containing quantitative models that study different aspects of the blood supply chain, and identifies several gaps in this literature. In particular, only eight of the 110 papers focus on the production stage. In this paper we address this research gap and present an integrated simulation-optimization model to support strategic and operational decisions in production planning in the blood supply chain.

The most common collection method is called whole blood donation, which consists of extracting approximately 450 ml of blood from a donor into a collection bag. There are

different types of collection bag, each yielding different blood products. The whole blood is centrifuged and, depending on the type of bag used for collection, is fractionated (split up) into different components such as red blood cells (RBCs), platelets, cryoprecipitate and plasma. An alternative collection method is apheresis, which directly withdraws a single blood component from a donor. Apheresis is considerably more efficient than fractionation, but has the disadvantages of higher costs and longer collection times. The chosen collection method largely determines the production method, with the exception of blood units collected using a quadruple bag. In this case there are two alternative fractionation methods, and a decision is normally made after the unit has arrived at the blood center.

Given the range of production alternatives, uncertainty in supply and demand throughout the year, and special features such as perishability, it is essential to develop efficient methods for production planning which consider the different collection methods, fractionation alternatives and donation rates. There is a trade-off between the indicators for outdates and stockouts in the blood supply chain: very large inventories of blood products can generate outdated units, but low inventories can cause stockouts, decreasing the service level (and potentially putting patients at risk). Furthermore, blood supply chain planning tools need to consider not only inventory policies that take into account uncertainty and seasonality, but also the trade-off between efficiency and cost for the different collection/production alternatives.

In this paper we present a model that combines discrete-event simulation (DES) with integer linear programming (ILP) to support decision making in the blood supply chain. The model includes several characteristics that have not been taken into account in previous research, for example multiple products and different collection/production methods, and the impact of variability. The model can be used in two modes: firstly at a strategic level, to enable blood center managers to evaluate different resource allocation policies, and secondly at an operational level, to set daily collection and production targets. The model outputs in both cases are the standard key performance indicators for blood supply chains: stockouts, outdates, number of donors, and production costs. In both modes, the ILP calculates the optimal required number of donors each day by

blood group and collection/production method, whereas the DES represents the daily operations of the blood center, incorporating uncertainty in supply and demand, based on probability distributions fitted from historical data routinely collected in all blood centers.

The DES does not depict the detailed minute-by-minute operations of the center, but aggregates these at a daily level. The ILP is run every day over a 7-day planning horizon: thus for example the ILP is run at the start of day 5 and produces collection/production targets for days 5 to 11. The DES then simulates the center's operations on day 5, based on a) the system state at the end of day 4 (i.e. the numbers of units of each blood product in stock, by age and blood type) and b) the optimal donor and production targets for day 5. At the start of day 6, the process repeats: the ILP is run for days 6 to 12, and the DES simulates the center's operations on day 6, based on the system state at the end of day 5 and the optimal targets for day 6.

In strategic mode, the combined DES/ILP model can be run for many months in order to evaluate different collection and production policies: the model is initialized by running the DES for a month to obtain the system state at the start of day 1. However in operational mode, the simulated system state information passed to the DES at the start of day t is replaced by "live" data from the blood center for day t-1. In this case no warm-up is required since real data will be used to initialize the system state at the start of day 1. Moreover, in operational mode only the collection/production plan for Day t will actually be implemented, since the ILP will be run again on Day t+1, potentially resulting in a different collection/production plan for that day depending on the real system state at the end of day t. The model is tested for three different scenarios which make increasingly realistic assumptions about a blood center's ability to achieve the desired optimum values. The results are compared with a baseline scenario which uses observed data and the collection/production rules used by a real blood center in Colombia.

Our computational results are obtained using data from the Hemocentro Distrital blood center in Bogota, Colombia. The blood supply chain in Colombia is decentralized and there are many public and private blood centers; in addition, some large public and

private hospitals also operate their own internal blood banks. The Hemocentro Distrital is the second largest blood center in Colombia. Annually, it collects about 40,000 blood units and supplies over 70,000 blood products to more than 18 hospitals. In our study period (July 2013 - June 2014), the total number of stockouts of RBCs was 9,490 units; however, in the same period, the outdated number of units was 1,989 for RBCs and 1,736 for platelets. This means that some of the collected units were not used while at the same time some hospital requests were not met. Hence, collection and production planning can be improved in order to make better use of resources, reducing both shortages and outdating. Our model addresses these problems. This paper is structured as follows. Section 3.2 describes the literature related to the collection and production stages as well as integrated models. Section 3.3 presents the detail of our framework, as well as a description of the simulation model and the mathematical formulation of the optimization model. Sections 3.4, 3.5 and 3.6 present some of the features of the case study, the description of the scenarios analyzed and the model results, respectively. Finally, Section 3.7 presents the main conclusions of this research, including modeling issues, as well as further extensions to this work.

3.2 Literature Review

In recent years the literature related to the blood supply chain has been increasing. However, some areas have received less attention than others. The blood supply chain can be split into four echelons or stages: collection, production, inventory and distribution. Traditionally, most research interest has focused on inventory policies, and the least-studied stage is production. Some papers have considered several echelons, so-called integrated models. In this section, the literature on the collection and production stages is presented, as well as integrated models for these stages.

3.2.1 Collection Stage

The literature in the collection stage covers various aspects such as the configuration of collection points, collection policies and collection methods, and special situations such

as disasters and emergencies. In Pratt & Grindon (1982) and Brennan et al. (1992), different configurations of collection points for different donor arrival rates are evaluated. Brennan et al. (1992) extend this work, considering staff allocation and working place policies. Both articles use simulation as the main methodology to measure the impact of changes in conditions through indicators such as the time taken in different stages of the collection process. In Michaels et al. (1993) different strategies of donor scheduling are studied. Other researchers have studied collection policies and collection methods and their impact on the performance indicators of the blood supply chain. Lowalekar & Ravichandran (2010) develop a simulation model to evaluate different collection policies. One of the main conclusions of this work is that it is not necessarily beneficial to collect as much blood as possible. Alfonso et al. (2012, 2013) also develop a simulation model aimed at determining the capacity and staff required. Two recent papers, Alfonso & Xie (2013) and Alfonso et al. (2014) present mathematical models for collection planning. The aim of the first model is to minimize products obtained from external suppliers. Madden et al. (2007) evaluate the impact of two different collection methods for RBCs, using fractionation and double red blood cells donation by apheresis (2RBC) (fractionation produces just one unit of RBCs while 2RBC produces two units). Ghandforoush & Sen (2010) use a nonlinear integer program to support the daily process of platelet production planning. Finally, Gunpinar (2013) minimizes the distance of collecting blood units from remote donors. Other papers such as Glynn et al. (2003), Sonmezoglu et al. (2005), Boppana & Chalasani (2007) and Jabbarzadeh et al. (2014) present quantitative models aimed at studying blood collection aspects of disaster and emergency situations. However, none of these studies have considered the multiple alternatives available for collecting blood and blood products, which is one of the key features of the proposed models.

3.2.2 Production Stage

As mentioned previously, the production stage has received little attention from researchers. Some articles have studied aspects such as production alternatives, single product production and platelet production as well as production capacity and internal

processes. The first studies that consider multiple products are presented by Deuermeyer & Pierskalla (1978) and Deuermeyer (1979) who develop an analytical model to minimize the production costs of RBCs and platelets. In this paper, production decisions are associated with different production processes and are defined according to the initial inventories of each product. Some of the production models have focused exclusively on single products. Sirelson & Brodheim (1991) use simulation to develop profile graphs, where inventory levels are associated with accepted shortage and outdating rates. Katz et al. (1983) propose an equation to define a platelets production function. This function is based on historical demand and deviations for each day as well as planned inventory and service levels. Finally, Ledman & Groh (1984) develop production planning rules considering demand mean, variability and collection schemes. This paper introduces concepts that had not been previously considered, such as different collection policies. Special attention has been paid to platelets in the past decade. Haijema et al. (2007), Haijema et al. (2009) and van Dijk et al. (2009) develop a Markovian model to represent decisions on production and inventories of platelets. Multiple periods, special periods such as weekends and different types of demand are included in the model. Dynamic programming and local search algorithms are used as solution methods, depending on the problem size. Finally, Baesler et al. (2011) present a simulation model to study capacity and support decisions on capacity expansion, in terms of resource utilization and internal waiting times and queues. Most of these studies consider only red blood cells or platelets. Our model considers the four main blood products as well as different fractionation alternatives and collection methods to obtain them.

3.2.3 Integrated Models

Most literature in the blood supply chain is focused on individual echelons and does not consider relationships between the different stages. For example, models for collection rarely consider production and distribution policies. A few, more recent, publications have aimed to connect donors with recipients by considering flows of blood and blood products throughout the supply chain. Different methodologies have been used, such as

simulation, optimization and hybrid approaches to study and improve the blood supply chain. One of the main approaches to represent and study the blood supply chain is discrete event simulation (DES). Page (1980*b*), Rytilä & Spens (2006), Katsaliaki & Brailsford (2007), Yegül (2007) and Baesler et al. (2014) use DES to evaluate and improve different aspects of the blood supply chain such as inventory allocation, recycling blood, crossmatching and mismatching rules, collection targets, and transshipments. The standard performance indicators used to measure improvements are the numbers of outdated units, stockouts and emergency orders, and of course cost. Another simulation paradigm used to study the blood supply chain is Monte Carlo simulation. Using this methodology, Lowalekar & Ravichandran (2011) consider different strategies, including fixed and variable collection quantities. In the production stages, the authors evaluate different fractionation rates. On the other hand, Simonetti et al. (2014) combine DES and Monte Carlo simulation to study different issuing policies, evaluating availability and shortage indicators. Mathematical programming is used by Nagurney et al. (2012) to optimize the whole blood supply chain. This model considers the blood supply chain as a network problem, defining different nodes, arcs and flows to represent the stages in the supply chain. An extension of this work is presented in Nagurney & Masoumi (2012), including discard rates and arc capacities. In addition, Abdulwahab & Wahab (2014) propose a combination of methodologies such as the newsvendor problem, linear programming and approximate dynamic programming to address the platelets inventory problem. Finally, multi-objective approaches and simulation optimization methodologies have been used: Lang (2010) uses a combination of simulation and heuristic methodologies to evaluate the impact of both transshipment and substitution.

3.3 Methodology

The combination of simulation and optimization is a powerful approach for capturing the complex features of supply chain systems. This approach can be implemented in various ways, depending on the simulation paradigms chosen. Examples can be found in Nikolopoulou & Ierapetritou (2012), Santoso et al. (2005) and Almeder et al. (2009) for agent-based simulation, Monte Carlo simulation and DES, respectively. In the blood

supply chain, optimization models have been used less frequently than in industrial supply chains. Approaches such as dynamic programming have been used in the blood supply chain to study the case of platelets, as seen in Haijema et al. (2007), Haijema et al. (2009) and more recently in Abdulwahab & Wahab (2014). The shelf life of platelets is only five days, making it possible to apply analytical techniques. However, the shelf life of red blood cells is 42 days, and thus the problem size is too large for exact solution, since the age of the products must be tracked throughout the planning horizon, greatly increasing the number of decision variables in the model. In addition, the combination of integrality constraints (since the decision variables include donors and blood units), uncertainty, multiple time periods and multiple products make it even more challenging to apply exact solution methods. On the other hand, DES models are ideally suited to representing complex stochastic systems of this nature, although of course there is no guarantee of finding an optimal solution with DES. The combination of simulation and optimization offers a practical way to handle complex decisions in the blood supply chain. The simulation model was developed using the Anylogic® simulation software package, probability distributions were fitted using @RiskTM and the optimization models were solved using the Java interface of the Gurobi Solver

3.3.1 Simulation-Optimization Framework

In our framework, as outlined in Section 3.1, simulation is used to represent the actual behavior of the real-world system, incorporating variability in donation and demand. Features such as perishability, blood type proportions and multiple products are included in the DES model. Mismatching and cross-matching are not included, since they only become relevant in the hospital when a specific request is made by a physician, and are thus outside the scope of this model. Optimization is used to support decisions concerning the required number of donors (either in total or broken down by blood group) and the associated collection and production methods, in order to minimize the production cost. The proposed methodology can be classified as an "Iterative Optimization-based Simulation (IOS)" according to the taxonomy proposed in Figueira & Almada-Lobo

(2014). In this case the simulation model implements (and hence evaluates) the solution obtained from the optimization model.

3.3.2 Assumptions

The model presented in this paper includes many assumptions. Firstly, some general assumptions:

- All the required data will be available on a daily basis.
- The collection teams will follow the collection goals obtained from the optimization model.
- Special cases such as natural disasters or epidemics that decrease historical donation rates are excluded.
- Demand follows historical patterns and can be predicted using standard forecasting techniques.

Secondly, some reasonable assumptions are made about donor arrivals and demand, as follows:

- Donor arrivals are distributed throughout the day, and follow historical rates by day of week.
- Donor blood types follow historical proportions.
- There is always sufficient capacity to process the target number of donors.
- Donors can be deferred, depending on the scenario analyzed.
- Donors from specific blood groups can be targeted and will donate.
- No additional donor campaigns are run other than normal daily collection.
- Demand can be partially satisfied. Hospitals always accept the products dispatched by the blood center.

- Demand follows historical behavior throughout the year, taking seasonality into account.
- Substitution of products is made at the hospitals.
- Returns of blood products to the blood center are not allowed.

3.3.3 Simulation – Optimization Interaction

Figure 3.1 depicts the interaction between the DES and the ILP. After initialization, the model runs interactively in one-day time steps with a 7-day planning horizon. This rolling horizon scheme helps to reduce the impact of uncertainty in the ILP model. The reason for a seven day period is to account for the fact that collection rates vary by day of week and other factors. In addition to the system state at the start of day t, the ILP also receives external information: whether collection is possible on days t,...,t+6 (for example, whether these days are working days or holidays), minimum inventory targets, proportions of donations by day of week and the predicted demand for days t,...,t+6. Based on this information, the ILP is run and the results (the optimum number of donors required by blood group and collection method) are sent to the simulation model. The DES model then simulates day t and passes the results (the system state at the end of day t) back to the ILP model ready for the start of day t+1. In strategic mode, the cycle then repeats until the end of the analysis period (one year in our experiments).

The optimal donor information from the ILP is treated in three different ways in the DES, depending on the scenario analyzed. In the first scenario, the required number of donors is broken down by blood group and collection method. In the second scenario we only consider the total number of donors, and the proportion of these donors allocated to each collection method. Finally, in the third scenario we only consider the donor proportions for each collection method. This is explained in detail in Section 3.5.

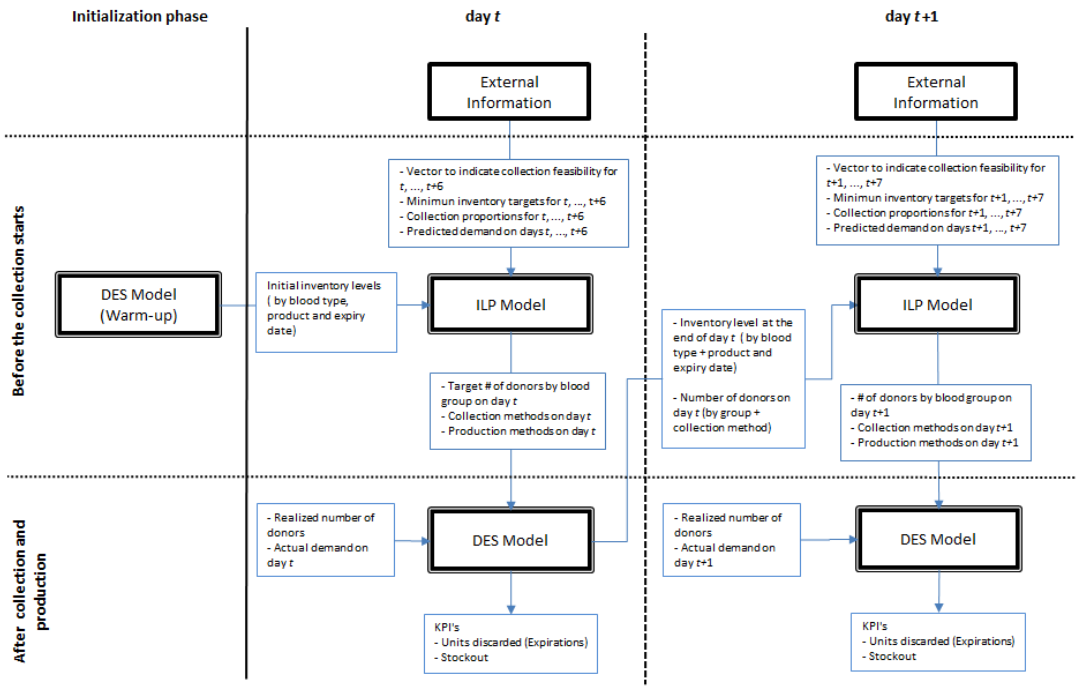


Figure 3.1: Simulation-optimization framework proposed for strategic level production planning in the blood supply chain.

In a real application used in operational mode, as previously stated, the simulation output at the end of day t is replaced by the live data from the real system. The ILP model must be run every day by the decision-maker responsible for collection before the collection starts. The results of the optimization model determine the collection goals for the teams and need to be shared with the production section of the blood center. For practical implementation, the optimization model would need to be integrated into the central information system of the blood bank in order to receive up-to-date information every time it is run. All the information required by the model is normally available in blood bank information systems and the routine periodic reports produced by blood centers.

3.3.4 Incorporating Variability

The sources of uncertainty, in the real system and in the model, relate mainly to demand for blood products and the arrival of donors at the collection stage. However, in our first set of experiments (see Section 3.5) both demand and donor arrivals are replaced by

empirical data, in order to compare the actual performance of the Hemocentro Distrital in the study period with the results that could have been achieved if our model had been applied. In the our second set of experiments, probability distributions are fitted to historical data on donor arrivals and the realized values are obtained by sampling.

3.3.5 DES Model

Figure 3.2 presents the flow diagram of the different stages in the DES model. The blood supply chain is highly complex, and each stage involves several interacting processes. Since this study focuses on daily collection and production policies, all transactions are aggregated on a daily basis. The simulation model represents a typical blood center that provides blood products for several demand points. The collection, production, inventory and distribution processes are included in varying levels of detail. As mentioned earlier, processes carried out in hospitals are not included, so the distribution stage in particular is modeled at a very high level.

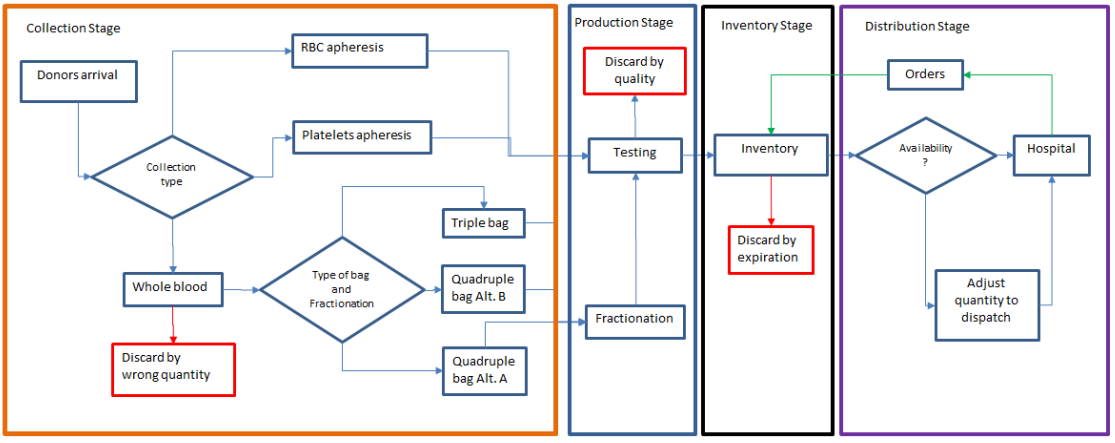


Figure 3.2: Flow diagram of the blood supply chain.

3.3.5.1 Collection Stage

Donors arrive and are assigned to a collection method according to the chosen scenario. The donor arrival rate corresponds to the historical data from the studied blood center. The collection alternatives are whole blood donation, RBC apheresis and platelets apheresis. For whole blood donations, the type of bag to be used is also considered, since

(with the exception of quadruple bags) the production processes depend entirely on the type of bag. Since whole blood collected in quadruple bags can be fractionated in two different ways, in our model this fractionation decision, alternative A or B, is made at the collection stage, as shown in Table 3.1. This is a very minor assumption in practice, and avoids the need for another index set which would greatly increase the problem size. Donor blood groups are defined according to historical donation rates in the blood center. A discard rate for whole blood units, based on historical data, is included before fractionation, since errors during collection can result in blood units that do not meet the volume requirements. The total number of units collected is proportionally reduced by this discard rate in order to obtain the final number of units that will proceed to the production stage.

Figure 3.3 presents a snapshot of the simulation model of the collection stage.

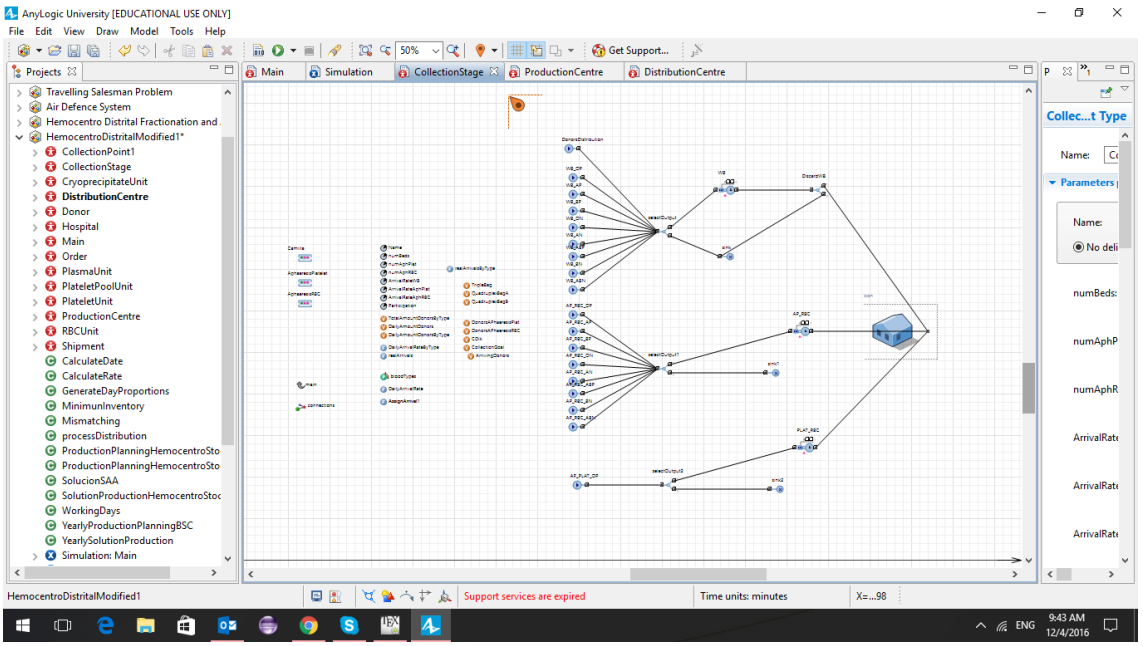


Figure 3.3: Snapshot of the simulation model of the collection stage.

3.3.5.2 Production Stage

The simulation of the production stage represents the testing and fractionation processes. Products obtained by apheresis do not need fractionation, but still go through the production stage for testing and quality control purposes. Historical discard rates

are applied here too, to represent the different reasons for discarding collected blood units during production, such as reactive tests and substandard quality. This stage also includes a period called quarantine, where the products are isolated while samples are tested in order to identify diseases and other defects. One unit of whole blood collected in a triple bag yields one unit of RBCs and one unit of plasma. For quadruple bags, Alternative A yields one unit of RBCs, one unit of plasma and one unit of platelets, whereas Alternative B generates one unit of RBCs and one unit of cryoprecipitate. Apheresis generates only one type of product. The production alternatives and the resulting number of units of each product are presented in Table 3.1. We note that, in general, apheresis for platelets can yield up to 12 standard units, but in the Hemocentro Distrital, normally only six units are collected.

Table 3.1: Blood products obtained in each process.

Process	**RBCs**	**Plasma**	**Platelets**	**Cryoprecipitate**
Triplex bag	1	1		
Quadruple bag – Alternative A	1	1	1	
Quadruple bag – Alternative B	1			1
RBC by apheresis	2			
Platelets by apheresis			6	

Figure 3.4 presents a snapshot of the simulation model of the production stage.

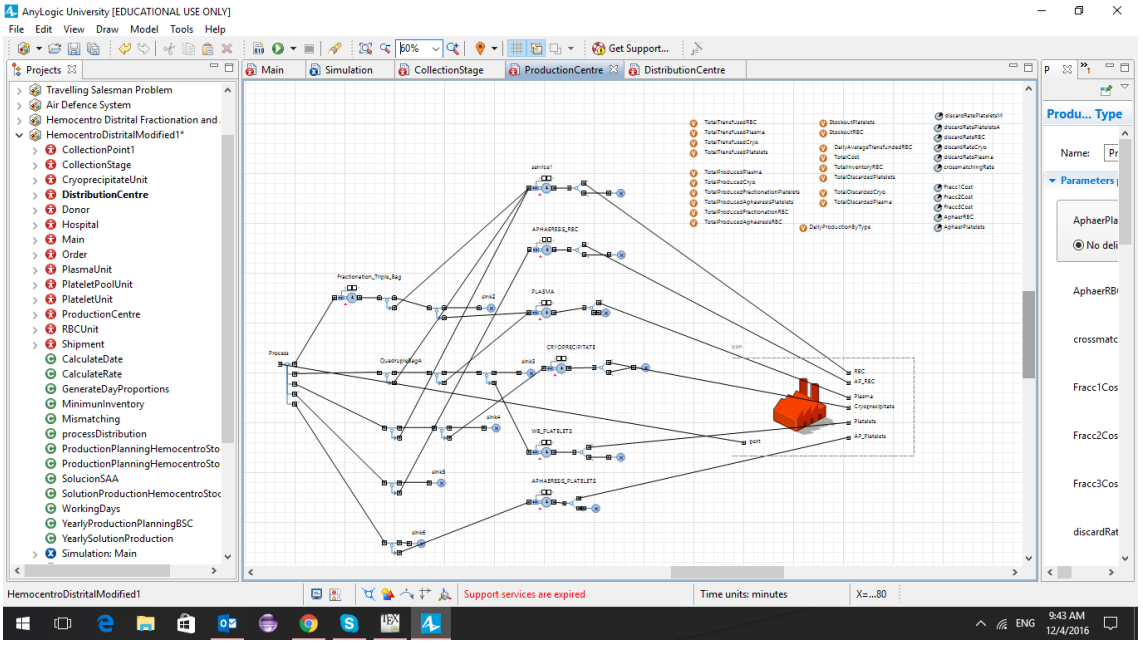


Figure 3.4: Snapshot of the simulation model of the production stage.

3.3.5.3 Inventory Stage

In the inventory stage, the daily operation of the inventory levels for each product is represented. After quarantine is complete (in our case study, at approximately 5:00 pm each day), products are added to the inventory and are available to be used. At the beginning of each working day, all outdated units of each product are removed from the inventory to be incinerated. In our case study, orders are normally received by 10:00 am and are dispatched throughout the day. However this level of detail is not captured in the model, which is concerned only with total transactions per day. Thus, for the purposes of production planning, demand is defined for each day as the sum of all individual orders, both normal and emergency. The products are dispatched based on a first-in-first-out rule. The inventory system is defined as periodic where the review period is one day. Inventory levels are checked daily and a replenishment order up to a level S is placed. The optimization model operates on a daily basis. It is possible to operate a periodic inventory system with a different review time period, but it is of course necessary to adhere to the shelf life constraints. Some hospitals use continuous inventory systems. In the case of blood centers, the most widely used system is periodical with one-day period Osorio et al. (2015), probably because this synchronizes with collection, discarding, and distribution, which all usually operate on a daily basis. Thus our model is generally applicable to most blood centers.

Figure 3.5 presents a snapshot of the simulation model of the inventory stage.

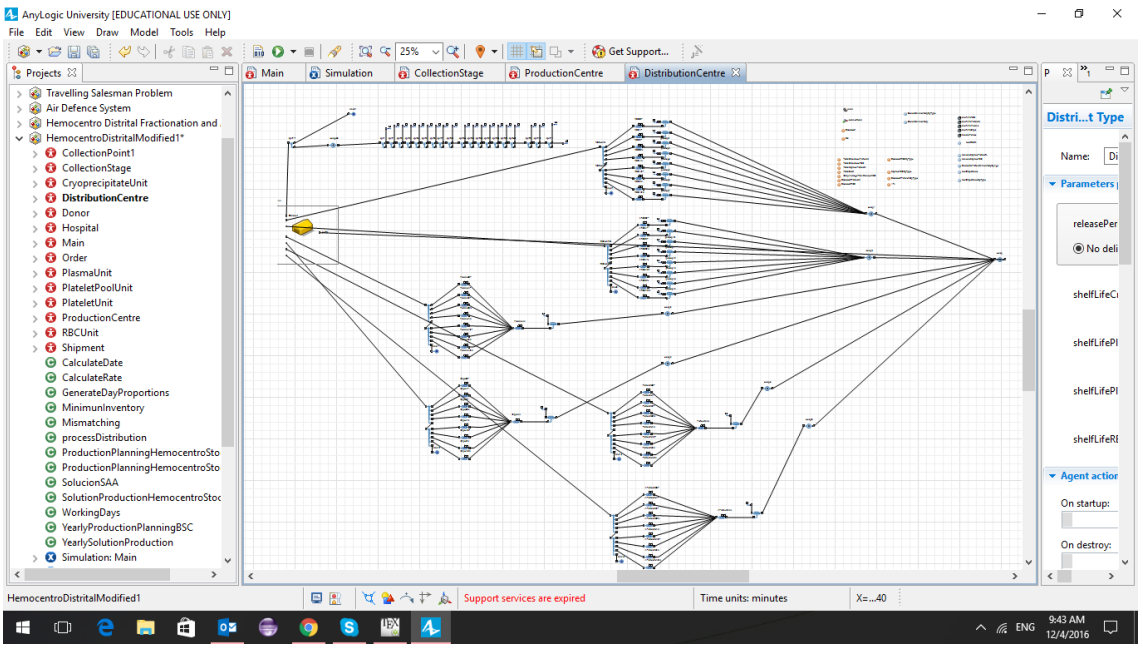


Figure 3.5: Snapshot of the simulation model of the inventory stage.

3.3.5.4 Distribution Stage

Finally, distribution is represented at a high level: only the dispatching rules are simulated, since the allocation of blood to individual patients is performed within hospitals and is outside the scope of our model. Given the critical importance of having some inventory on hand at all times in the blood center, a minimal safety stock is defined for each product. The dispatching rule states that, for every day, the maximum quantity that can be dispatched is the difference between the available quantity and the minimum stock (S) for each product. The choice of the values of S for different blood products is a managerial decision and is an external parameter in our model.

Figure 3.6 presents a snapshot of the simulation model of the distribution stage.

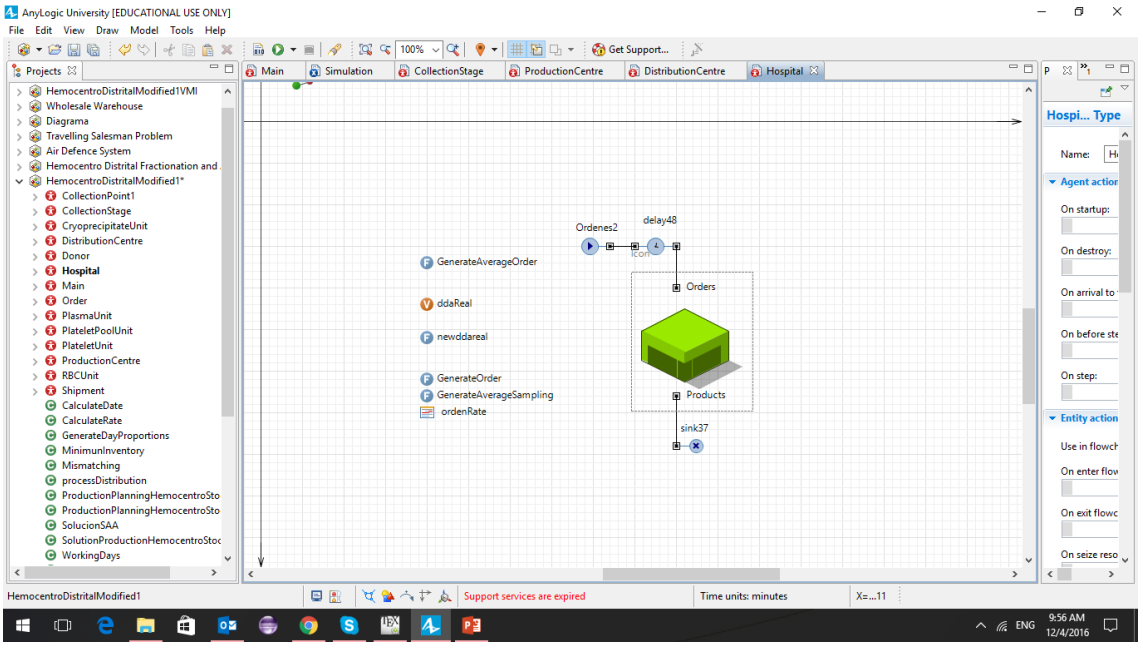


Figure 3.6: Snapshot of the simulation model of the distribution stage.

3.3.5.5 Data Required by the Model

The information required to run the model consists of both historical and current data relating to the analyzed system. At the collection stage, the model needs information related to the structure and capacity of the collection points, historical data of donor arrivals for each day, by blood group, the collection methods used, and the discard rates. At the production stage, the model requires information on the capacity of the production centers, the efficiency of the production processes, the production costs and inventory policies. At the inventory and distribution stages, it is necessary to know daily historical demand for each blood product by blood group and current inventory levels of each product. Historical data on donor arrivals by blood group and demand for blood productions allow patterns to be identified over time, and probability distributions to be fitted to represent the uncertain aspects of the system. On the other hand, discard rates, shelf life information and inventory policies define some of the model parameters which represent a specific blood center. Finally, in order to compare the performance of the proposed models, knowledge of current costs, outdate and shortage rates, and number of donors required is needed. We note that all these data are normally routinely

recorded and stored by blood centers, and would be readily available (as they were in our case study).

3.3.6 ILP Model

The optimization model supports decisions on collection and production. The model considers blood group proportions, demand, inventory, capacity and shelf life constraints, and seeks to optimize a cost function composed of production costs, penalties for expired units, number of stockout units and violation of the blood group proportionality constraint. The decision variables are the number of donors required per day, by blood group and production method. Auxiliary variables are defined to calculate production and inventories to ensure the correct balance of products throughout production planning.

Definition of Sets

K	=	Collection alternatives – indexed by k.
J	=	Products required – indexed by j.
T	=	Planning horizon – indexed by t.
I	=	Blood types – indexed by i.
S	=	Set of values for the shelf life alternatives of platelets – indexed by s.
P	=	Set of types of platelets – indexed by p.

Model Data (Information Provided)

A_{ij}	=	Number of donors of blood type i served by process k on the previous day, $i \in I$, $j \in J$.
B_{jt}	=	Predicted demand for product j in period t, $j \in J$, $t \in T$, [Units of product]. This parameter is obtained from the actual forecast demand B'_{jt} after taking into account the discard rate α_j, and is calculated as $B_{jt} = B'_{jt}(1 + \alpha_j)$, $j \in J$, $t \in T$.
C_{ikj}	=	Number of units of product type j obtained from applying process k to a unit of blood type i, $i \in I$, $j \in J$, $k \in K$.

D_i = Proportion of blood type i in the population studied, $i \in I$.

E_k = Collection cost for one donor assigned to collection method k, $k \in K$ [US$].

F = Daily capacity for serving whole blood donors, on days when collection is possible.

G = Daily capacity for serving RBC apheresis donors (as above).

H = Daily capacity for serving platelets apheresis donors (as above).

α_j = Historical discard rate of product j, $j \in J$.

L = Penalty cost for each unit of product not available [US$].

M_j = Minimum inventory of product j, $j \in J$. (This parameter is equivalent to S, as defined in Section 3.5.3.).

N_j = Initial inventory of product j, $j \in J$ [Units].

O_t = Observed proportion of donations in period t, $t \in T$. Each day of the week has a different behavior, but the order varies since it is a rolling horizon model.

Q = Penalty cost for each unit of platelet expired [US$].

R_t = 1 if it is possible to collect blood in period t, 0 otherwise, $t \in T$. This parameter represents the possibility of collecting blood for each day of the planning horizon, given public holidays and special days where collection is not carried out.

X_{ps} = Initial inventory of type p platelets with s remaining days of shelf life, $p \in P$, $s \in S$. [Units]. Shelf life constraints are only considered for platelets.

V = Maximum daily number of donors.

W = Maximum weekly number of donors.

Z = Penalty for violating the soft constraint on proportionality (Constraint (3.15)) [US$].

Decision Variables

x_{ikt} = Required number of donors of blood type i, for collection using process k in period t, $i \in I$, $k \in K$, $t \in T$.

Auxiliary Variables

q_{jt} = Number of units of product j produced in period t (and available in period t+1), $j \in J$, $t \in T$.

w_{jt} = Number of units of product j in inventory at the end of period t (and available in period t+1), $j \in J$, $t \in T$.

y_{jt} = Estimated stockout of product j in period t, $j \in J$, $t \in T$ [Units].

δ_{it}^{-} = Slack variable for the soft constraint of blood type i in period t, $i \in I$, $t \in T$.

δ_{it}^{+} = Surplus variable for the soft constraint of blood type i in period t, $i \in I$, $t \in T$.

p_{pt} = Estimated stockout of platelets of type p in period t, $p \in P$, $t \in T$ [Units].

r_{pst} = Number of platelets of type p with shelf life s in the inventory in period t, $p \in P$, $s \in S$, $t \in T$.

u_{pst} = Number of platelets of type p with shelf life s in period t used to meet demand, $p \in P$, $s \in S$, $t \in T$.

z_{pt} = Number of platelets of type p expired in period t, $p \in P$, $t \in T$.

Objective Function

$$\min \quad \sum_{i\in I}\sum_{k\in K}\sum_{t\in T} E_k x_{ikt} + Q\sum_{t\in T}\sum_{p\in P} z_{pt} + L\sum_{t\in T}\sum_{j\in J} y_{jt} + Z\sum_{t\in T}\sum_{i\in I}\delta_{it}^{+} \tag{3.1}$$

The first term in Equation 3.3.6 computes the production cost while the second and third terms contain the penalties for outdated units and stockouts, respectively. The

last term penalizes the violation of the proportionality constraint.

Constraints

$$\sum_{i \in I} \sum_{k=0,1,2} x_{ikt} \leq FR_t, \quad \forall t \in T \tag{3.2}$$

Constraints (3.2) guarantee that the collection of whole blood donations does not exceed the capacity available. For RBCs and platelets obtained from apheresis, the constraints become $x_{i3t} \leq GR_t \ \forall i \in I, \ \forall t \in T$ and $x_{i4t} \leq HR_t \ \forall i \in I, \ \forall t \in T$, respectively.

$$q_{j0} = \sum_{i \in I} \sum_{k \in K} A_{ik} C_{ikj}, \quad \forall j \in J \tag{3.3}$$

$$q_{jt} = \sum_{i \in I} \sum_{k \in K} x_{ikt-1} C_{ikj}, \quad t \geq 1, \forall j \in J \tag{3.4}$$

Constraints (3.3) and (3.4) represent the production balance constraints for $t = 0$ and $t > 0$ respectively. The actual number of donors on the previous day is multiplied by the parameter C_{ikj} that defines the quantity of each product to be obtained from the different alternatives. For $t = 0$, actual information about the collection on the previous day is assumed to be available. For $t > 0$, the production is a function of the collection target of the previous day. Products produced in period t will only become available in period $t + 1$, because of the production and testing processes.

$$w_{j0} - y_{j0} = N_j - B_{j0}, \quad t = 0, j \neq 16, 17 \tag{3.5}$$

$$w_{jt} = w_{jt-1} + q_{jt-1} + y_{jt} - B_{jt}, \quad t > 0, j \neq 16, 17 \tag{3.6}$$

In Constraints (3.5) and (3.6) the initial inventory is decreased by the quantity used (demand – stockout) and this is equal to the number of units in inventory at the end of the period (which will be available at the beginning of the next period). In periods where t > 0 the constraint balance is modified by the addition of the number of units produced on the previous day. Platelets (indexed by $k = 16$ and $k = 17$) are excluded

from this balance constraint since additional features such as remaining shelf life must be considered.

$$z_{p0} = X_{p0} - u_{p00}, \quad \forall p \in P, s = 0, t = 0 \tag{3.7}$$

$$r_{ps-1,0} = X_{ps} - u_{ps0}, \quad \forall p \in P, s > 0, t = 0 \tag{3.8}$$

$$z_{pt} = r_{p0t-1} - u_{p0t}, \quad \forall p \in P, s = 0, t > 0, t \in T \tag{3.9}$$

$$r_{ps-1t} = r_{pst-1} - u_{pst}, \quad \forall p \in P, s \neq 0, 4, t > 0, t \in T \tag{3.10}$$

$$r_{0s-1t} = r_{0st-1} + q_{16t-1} - u_{0st}, \quad s = 4, t > 0, t \in T, j = 16, p = 0 \tag{3.11}$$

$$r_{1s-1t} = r_{1st-1} + q_{17t-1} - u_{1st}, \quad s = 4, t > 0, t \in T, j = 17, p = 1 \tag{3.12}$$

Constraints (3.7) – (3.12) define the balance of platelets considering inventory, production, expiration and use. In Constraints (3.7) and (3.9) ($s = 0$) the number of units available at the beginning of the period is decreased by the number of platelets used with a shelf life of zero; the remaining quantity will be outdated and will not be available in the next period. In Constraints (3.8) and (3.10), the number of units available is also decreased by the quantity used; however, in this case, the remaining quantity will be the initial inventory in the next period. The shelf life of the platelets in Constraints (3.8), (3.10), (3.11) and (3.12) is updated at the end of the period; the new shelf life will be $s-1$. Finally, for the shelf life index $s = 4$ (Constraints (3.11) and (3.12), the constraint is slightly different, since a new value q_{lt-1} is incorporated into the balance constraint. This value corresponds to the quantity of platelets produced in the previous period.

$$\sum_{s \in S} u_{0st} - p_{0t} = B_{16t}, \quad \forall t \in T, j = 16, p = 0 \tag{3.13}$$

$$\sum_{s \in S} u_{1st} - p_{1t} = B_{17t}, \quad \forall t \in T, j = 17, p = 1 \tag{3.14}$$

Since platelets have different shelf lives, we include an auxiliary variable u_{pst} to specify the number of units of platelets of different ages. This allows the inventory to be updated

while tracking the age of platelets. Constraints (3.13) and (3.14) define the number of units used as demand minus stockout.

$$\sum_{k\in K} x_{ikt} - \sum_{i'\in I}\sum_{k\in K} x_{i'kt} D_{i'} + \delta_{it}^{-} - \delta_{it}^{+} = 0, \quad \forall i \in I, \forall t \in T \tag{3.15}$$

$$\sum_{k\in K} x_{ikt} \leq D_i V, \quad \forall i \in I, \forall t \in T \tag{3.16}$$

$$\sum_{i\in I}\sum_{k\in K} x_{ikt} \leq WO_t, \quad \forall t \in T \tag{3.17}$$

$$w_{jt} \geq M_j, \forall j \in J, \forall t \in T \tag{3.18}$$

$$x_{ikt},\ y_{jt},\ p_{pt},\ r_{pst},\ u_{pst},\ z_{pt},\ q_{jt},\ w_{jt} \in \mathbb{Z}^{+},\ \delta it^{-},\ \delta it^{+} \in \mathbb{R}^{+} \tag{3.19}$$

Constraints (3.15) and (3.16) guarantee one of the most important features of the blood supply chain: blood group proportionalities need to be met when production planning is considered. Constraints (3.15) guarantee the proportionality for each blood type for every day of the 7-day planning period. In order to keep the integrality of the variables, the constraint is relaxed by adding slack and surplus variables. The surplus variable is penalized in the objective function to try to maintain the proportionality conditions. Constraints (3.16) are introduced in order to control the quantity collected daily for each type. In addition, Constraints (3.17) limit the collection for each day according to historical rates. These constraints are necessary since, historically, days might have different behaviors. For instance, in the data obtained for the case study, the collection is higher on Wednesdays and Thursdays, while weekends are the lower collection days and the collection planning must to consider this feature. Finally, the minimum inventory is defined by Constraints (3.18) and domains are given in Constraints (3.19).

The complete optimization model is presented as follows:

$$\min \quad \sum_{i\in I}\sum_{k\in K}\sum_{t\in T} E_k x_{ikt} + Q\sum_{t\in T}\sum_{p\in P} e_{pt} + L\sum_{t\in T}\sum_{j\in J} y_{jt} + Z\sum_{t\in T}\sum_{i\in I}\delta_{it}^{+}$$

subject to: (3.2) - (3.19).

3.4 Case Study

The Colombian National Blood Bank Network is comprised of 87 blood banks and 414 points for transfusion services (INS 2013). Blood banks differ in size and types of services offered. Large public and private blood centers supplying products for several hospitals can be found in the large cities. Blood banks are also located within hospitals. The distribution centers are usually co-located with the blood banks. The Colombian system is highly decentralized, compared, for example, with the UK National Blood Service network, which consists of five large production centers and 15 stock holding units across the country (Woodget, 2014). Another feature of the Colombian system is the range of collection strategies across the country; each region defines the collection goals for blood and blood products using local decision rules. The highest proportion of platelets collected by apheresis in 2012 is represented by the Valle del Cauca region with 93%, followed by Antioquia with 42%. However, most regions collect platelets from whole blood donations. On the other hand, the highest proportion of RBCs produced using apheresis processes is represented by the Tolima region with 8.24%, followed by 6.26% from Bogota. Again, most regions obtain RBCs exclusively from whole blood donations.

The Hemocentro Distrital comprises three main service areas: blood bank, tissue bank and cord blood bank. It is the second largest blood center and the unique multipurpose tissue bank in Colombia. The blood bank section is responsible for supplying blood products to more than 33 institutions, both public and private; however, priority is given to public hospitals in Bogota. During the analysis period (June 2013 to June 2014), 77,309 units of products were ordered, of which 56.6% were RBCs, 22.2% platelets, 19.2% plasma and 1.87% cryoprecipitate. The months of January and February are atypical: donations in these months are usually lower and the blood center can only meet part of the total demand. Therefore, the hospitals increase the quantity ordered, creating a distortion in real demand. The blood group proportionality in the observed data at the collection stage is as follows: O+ 60.9%, A+ 23%, B+ 7.92%, O- 4.22%, A- 1.72%, AB+ 1.54%, B- 0.51%, AB- 0.11%. In the case study system, hospitals can choose between products obtained by apheresis and those obtained from fractionation, and hence

demand for these products is independent. During the study period, although apheresis collection processes were in use, information about demand for products obtained by apheresis was not available. Nevertheless, apheresis collection methods are included in the model for the sake of generality. In other blood service systems, it is possible to meet demand using products obtained from either fractionation or apheresis processes.

Quantitative information for modeling purposes was obtained from the information systems of the blood center as well as monthly indicator reports. Interviews conducted with the staff of the blood center were used to validate and to adjust the simulation model. Daily information about collection, including blood groups, demand and shipments for each product was obtained for the period June 2013 to June 2014. Monthly information about discard rates, shortage and outdating rates were also obtained. In order to generate a realistic initial inventory considering the age of the products, the model used a one-month warm-up period, without including demand. The results obtained from this warming-up period were validated with the staff. The collection behavior is different for each day of the week. In order to represent this feature, probability distributions were fitted for each day (Appendix B). A monthly adjustment factor was also applied to the values generated in order to represent the monthly seasonal behavior in the collection stage. In addition, a probability distribution was fitted for each product for each day, with the exception of cryoprecipitate where actual information was used in all the scenarios. In the case of blood groups, proportionality rates were applied for both collection and demand. The indicators presented in the results section were generated using 100 iterations of one year for each scenario; the values presented were calculated using 95% confidence intervals. Since the ILP model is deterministic, it should be noted that the confidence intervals presented are calculated based on the randomness from the DES model.

The optimization model applied to our case study contains 1099 variables of which 987 are integer, and 664 constraints.

3.5 Scenarios

The model was tested for three different scenarios which make increasingly realistic assumptions about a blood center's ability to achieve the desired optimum values generated by the ILP:

- Scenario 1A: The blood center is able to recruit the optimal number of donors, by blood type and collection method
- Scenario 2A: The blood center can recruit the optimal number of donors but by collection method only
- Scenario 3A: The blood center can only control the optimal proportions for each collection method

It should be noted that different optimization models can be developed for Scenarios 2A and 3A. The results of applying different optimization models could improve the results obtained for Scenarios 2A and 3A presented in Section 3.6.

The results obtained from these three scenarios are compared with the KPIs from a baseline scenario which uses the observed empirical data and the real decision rules in operation at the time in the Hemocentro Distrital. Table 3.2 presents the data used in the simulation of each scenario. With the exception of scenarios 1A and 2A, daily donor arrivals are obtained from the historical data from the blood center. The demand in all four scenarios is the actual observed demand for each product type, by blood group.

Scenario 1A represents an idealized situation, since it assumes that each day, a blood center is able to recruit the precise number of donors by blood group specified by the ILP model. In practice it is impossible to have total control over the number of donors by blood group. However, this scenario helps decision-makers understand the importance of taking blood groups into account, and there are practical steps that blood centers can take to get closer to these ideal collection targets. They can target advertising at specific blood groups; they can defer donors whose blood type is not required at the time; and they can offer non-financial rewards for donation, e.g. gifts and souvenirs. Moreover, in

Table 3.2: Summary of scenarios: data used in simulation.

Scenario	**Total number of donors**	**Donors by blood group**	**Collection method**	**Demand**
Baseline	Observed data	Observed data	Observed data	Observed data
1A	Determined by the ILP model	Determined by the ILP model	Determined by the ILP model	Observed data
2A	Determined by the ILP model	Proportions in the observed data	Determined by the ILP model	Observed data
3A	Observed data	Observed data	Determined by the ILP model	Observed data

countries where donors are paid, these incentives can be straightforward cash payments. We shall see that system performance improves considerably when collection is close to the results determined by the ILP model.

Scenarios 2A and 3A test the robustness of the ILP model in more realistic settings, since scenario 1A is almost certainly unachievable in practice. In scenario 2A, we only consider the total number of donors for each collection method, irrespective of blood group; this implies that no action is carried out to target the blood groups specified by the ILP. In this scenario, simulated donors are assigned blood groups sampled at random, following the observed proportions in the data. Finally, in scenario 3A the ILP results are used exclusively to define the proportion of donors assigned to each collection method; this means that no action is carried out to recruit even a target number of donors, let alone by blood group. In this scenario the numbers of simulated donors are simply the observed numbers in the data, and they are assigned blood groups in the same way as for scenario 2A. The results from these three scenarios show what would have happened if the ILP model had been fully or partially applied in the Hemocentro Distrital during the study period.

In order to test whether the model can be generalized to other time periods, the results for three new scenarios (1B, 2B and 3B) are presented in Section 6.5. In this case, the observed data for donor arrivals are replaced by samples from probability distributions

fitted to the data. The results obtained using the distributions are very similar to those using actual data. This means that the analysis presented for scenarios 1A, 2A and 3A also applies for scenarios 1B, 2B and 3B respectively.

3.6 Results and Discussion

3.6.1 Stockouts

Given the life-critical nature of blood products, stockouts are probably the most important indicator to measure blood supply chain performance. In the Hemocentro Distrital, demand for RBCs is considerably greater than supply. One of the reasons for this is that hospitals are risk-averse and overestimate requirements when they place orders. Table 3.3 shows the magnitude of stockouts in each scenario and the percentage improvement over the baseline, with 95% confidence intervals. The optimization model improves this indicator for all products in every scenario (shown by the green shading). The best results are obtained in the "ideal" scenario 1A. The percentage improvement for RBCs and platelets are slightly higher in scenario 3A than in 2A, since in scenario 2A the ILP specifies a lower number of donors than in reality (see Section 3.6.3). In all three scenarios a larger number of donors are assigned to platelet collection methods, and thus more platelets are produced and the number of stockouts is lower. However, this also causes deterioration in the outdating indicator, as we shall see in Section 3.6.2. Finally, use of the ILP totally eliminated stockouts of plasma and cryoprecipitate.

Table 3.3: Results: stockouts.

Scenario	**Stockouts (units)**				
		RBC	Platelets	Plasma	Cryoprecipitate
Baseline		**9490**	**185**	**74**	**292**
1A	95% CI	7948 ± 29.8	110 ± 9.3	0 ± 0	0 ± 0
	% improvement	16.3%	40.3%	100.0%	100.0%
2A	95% CI	9006 ± 24.9	60 ± 5.2	0 ± 0	0 ± 0
	% improvement	5.1%	67.6%	100.0%	100.0%
3A	95% CI	8894 ± 22.3	53 ± 5.8	0 ± 0	0 ± 0
	% improvement	6.3%	71.2%	100.0%	100.0%

3.6.2 Outdated Units

The number of expired units is another important KPI for blood supply chains. Collecting blood is costly, and moreover donors do not like to think that their blood is being wasted: high expiration rates can have an undesirable impact on future donations. Results obtained for the expiration indicator are presented in Table 3.4. The ILP improves the expiration rate for RBCs in all three scenarios: the improvement is greater in scenario 3A than in scenario 2A, since in scenario 3A the number of donors by blood group follows the real observed data, which contains implicit empirical decisions that avoid collection for blood groups that are not required at the time. In contrast, in scenario 2A the blood groups are defined by strictly applying the blood group proportions from the historical data to a target number of donors.

Expiration is more critical for platelets, given their short shelf life. Expired platelets are lower in scenarios 1A and 2A, but higher in scenario 3A, because in this scenario the quantity of collected blood is not determined by the ILP (real data are used) and just the proportions of collection methods are applied. Clearly, if the quantity collected is too large there will be a surplus of final products which is critical in the case of platelets given their short shelf life.

Table 3.4: Results: outdates.

Indicator (units)	Baseline	**Scenario 1A**		**Scenario 2A**		**Scenario 3A**	
		95% CI	%	95% CI	%	95% CI	%
Outdated RBC	1989	33 ± 0.7	98.3%	1182 ± 20.7	40.6%	1064 ± 12.5	46.5%
Outdated Platelets	1736	1152 ± 23.7	33.6%	1349 ± 20.3	22.3%	1875 ± 28.6	-8.0%

3.6.3 Number of Donors

Table 3.5 presents the average number of donors, by blood group. The results show a modest improvement in the number of donors required. We note that in systems where demand can be supplied using both apheresis and fractionation, this indicator can be improved considerably. However, in our case the Hemocentro Distrital only uses

fractionation. Scenario 3A uses exactly the same number of donors as the baseline. The parameter W in the ILP limits the total number of donors per week, since the aim is to achieve an improvement without using additional resources. It can be seen that the model is able to reduce donor numbers slightly, in addition to improving the stockout and expiration KPIs.

Table 3.5: Results: number of donors.

Type	O+	A+	B+	O-	A-	AB+	B-	AB-	Total	Imp.*
Base Scenario	23541	8896	3059	1629	663	593	197	41	38619	
1D	24583	8141	2780	1884	614	176	0	0	38178	1.1%
2D	23920	9022	2084	1644	684	595	198	40	38186	1.1%
3D	23541	8896	3059	1629	663	593	197	41	38619	0

*Improvement

3.6.4 Costs

The total cost comprises the production cost, the stockout cost and the outdate cost. The results for each type of cost are presented in Table 3.6. In scenario 3A the production cost is slightly increased, because the number of donors is not controlled by the optimization model. The stockout and expiration costs are considerably reduced in Scenario 1A. The actual costs in the baseline scenario are not shown, for reasons of confidentiality. Again, the results depend on the extent to which the blood center is able to implement the recommendations from the ILP model. Scenario 1A achieves the greatest improvement in all the indicators, which implies that decision-makers must try to take blood groups into account when planning collection and production strategies.

Table 3.6: Results: costs.

Type of cost	**Scenario**		
	1A	2A	3A
Production Cost	1.22%	1.06%	-0.28%
Stockout Cost	17.04%	6.14%	7.32%
Expiration Cost	68.20%	32.07%	21.11%
Total Cost	4.13%	2.05%	1.05%

3.6.5 Generalizing the Model for Other Time Periods

In order to evaluate the performance of the model for different time periods, probability distributions were fitted for the donor arrival rates (see Appendix B) and used to replace the observed data from the study period as used in scenarios 1A, 2A and 3A. The same three implementation levels of the ILP outputs are analyzed, in three new scenarios 1B, 2B, and 3B. The results are consistent and are very similar to those obtained in scenarios 1A, 2A and 3A. The results are summarized in Table 3.7, which shows mean absolute values with 95% confidence intervals and mean % improvement over the baseline scenario.

Table 3.7: Summary of results with stochastic donor arrivals.

Indicator (units)	Baseline	**Scenario 1A**		**Scenario 2A**		**Scenario 3A**	
		95% CI	%	95% CI	%	95% CI	%
Stockout RBC	9490	7874 ± 101.4	17%	8960 ± 116	5.6%	8868 ± 134.9	6.6%
Stockout Platelets	185	76 ± 11.5	58.8%	47 ± 8.8	74.6%	108 ± 16.9	41.7%
Stockout Plasma	74	0 ± 0	100%	0 ± 0	100%	0 ± 0	100%
Stockout Cryop.	292	0 ± 0	100%	0 ± 0	100%	0 ± 0	100%
Outdated RBC	1989	125 ± 9.7	93.7%	1249 ± 34.6	37.2%	1224 ± 49.1	38.5%
Outdated Platelets	1736	941 ± 41.2	45.8%	1067 ± 47.6%	38.5%	1455 ± 63	16.2%
Number of Donors	38619	38167 ± 8.2	1.2%	38160 ± 8.4	1.2%	38671 ± 131.7	-0.1%
Total Cost US$ (M)		**4.2%**		**2.2%**		**0.8%**	

3.6.6 What-if Analysis

The results presented in Sections 3.6.1 – 3.6.5 are obtained using the actual weekly capacity (based on historical data). However, there is a large gap between supply and demand. Part of this gap is explained by demand overestimation in January and February, as discussed in Section 3.4. The other part corresponds to stockouts in other months. In order to evaluate the impact of variability in the number of donors and collection capacity, we now present the results for a further set of scenarios in which two further modifications are introduced with the aim of better matching supply and demand. We have previously seen that the best results are obtained in scenarios 1A and 1B, which

(unrealistically) assume that the number of donors in the DES is exactly equal to the optimal value of the variable x_{ikt}. Therefore we now assume the number of donors is a random sample from a uniform probability distribution with limits

$$\sum_{k \in K} x_{1kt} \pm 10\%$$

The collection method for each donor is assigned according to the original proportions in the data. Secondly, the weekly collection capacity (represented by the parameter W in the ILP problem) is also allowed to vary from –40% to +40% of the original value, in steps of 10%. Figure 3.7 presents the percentage improvements in all KPIs, giving the decision-maker a better overview of the impact of variation in the weekly collection capacity. The x-axis in 3.7 is the value of W, and the y-axis is the % improvement over the baseline. The results correspond to the mean of 30 iterations of the simulation model.

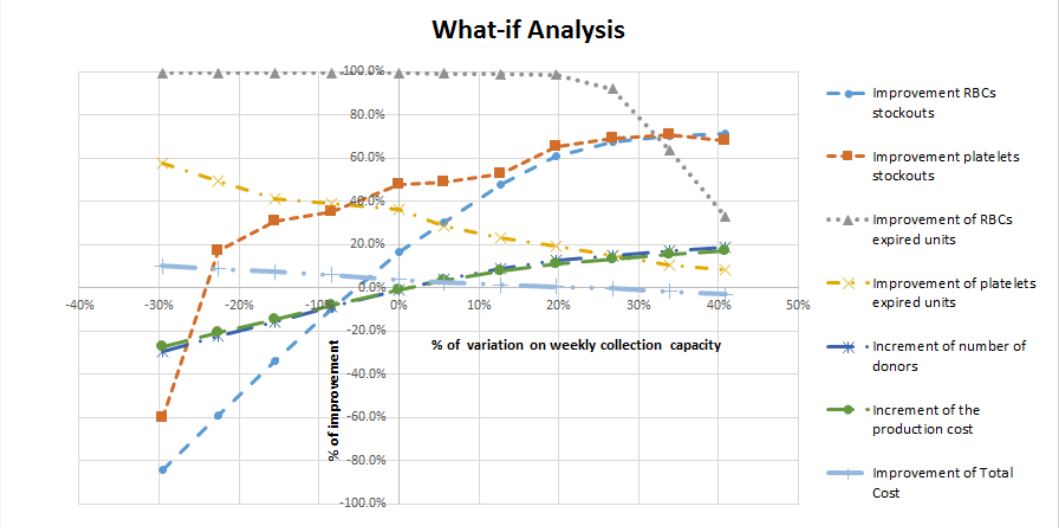


Figure 3.7: Performance indicators when weekly collection capacity is varied.

Since in the case of the Hemocentro Distrital there is already a gap between demand and supply, those strategies in which W is decreased may be disregarded by the decision-maker. Further conclusions can be drawn from Figure 3.7, of which perhaps the most relevant is that the Hemocentro Distrital can considerably improve its performance indicators, without increasing the total cost, by using the proposed ILP model to plan

collection and production. When the weekly collection capacity is increased, the production cost also increases since more collection and processing are carried out; however, this leads to a reduction in stockouts which compensates for the increased production cost in the total cost. Nevertheless, the improvement in the stockout KPI is not linear, since demand in some periods is overestimated and thus these stockouts are not "real" and cannot be covered even by increasing the weekly collection capacity. Increasing collection also results in a deterioration of the outdating indicator. Nevertheless, in every case where collection capacity is increased, the outdate indicators in the simulation are improved over the baseline.

3.7 Conclusions and Further Research

The blood supply chain continues to be an active research topic. Despite the increasing number of publications, some stages and topics, such as production and collection planning, have been studied less than others. The model presented in this paper extends the research in these areas.

The optimization model has improved supply chain performance in a range of different scenarios, with or without considering donor blood groups, and taking into account variability in donor arrivals, but including the collection/production method as a decision variable. Through the use of simulation, we have shown that the best results are obtained when the collection quantities are closest to the optimal numbers of donors, *by blood group*, determined by the optimization model.

The combination of simulation and optimization in the blood supply chain allows modeling and analysis of aspects that could be intractable using only one methodology. This integration offers a robust framework for modeling special features of the blood supply chain. In addition, the impact of uncertainty can be reduced by incorporating real-time information during the planning process. Rolling horizon models provide a means of including live information in the decision-making process. The proposed model uses a large amount of information such as donations, demand, discard rates, costs, and inventory levels; however, this information is usually available in all blood banks. Currently

blood bank information systems store very detailed information including that used here, as well as additional information regarding test results, and tracking methods for each unit of product.

The active participation of the Hemocentro Distrital throughout this project was very important: many discussions were required to understand the operational details and ensure that the models were a good representation of the real system. In view of the encouraging results, the Hemocentro Distrital is interested in starting a pilot for the proposed model, initially as a spreadsheet model and then, depending on the outcome, as an integrated module in its main information system. In terms of implementation, the most efficient way would be to integrate the optimization model into the Hemocentro Distrital's central information system. When the collection targets obtained from the model are assigned to the collection teams, the decision-maker would also need to bear in mind the specific characteristics of the chosen collection locations: the model is only a tool to support a human decision-maker, and such decisions may need to be modified in practice depending on circumstances. The optimization model solves in seconds in the commercial solver used.

Finally, the models presented in this paper can be extended in several ways. Inclusion of mismatching for internal blood banks in hospitals, multiple objective functions, prioritization of demand points and staff shift planning can all complement the model presented. This model represents a typical blood center, which operates independently from hospitals and demand points. It could be adapted for other blood supply chain topologies, but for blood banks in hospitals, the model would need to be adjusted to include compatibility of products.

Chapter 4

Whole Blood or Aphaeresis Donations? A Multi-Objective Stochastic Optimization Approach

Abstract

Several collection and processing alternatives are available in the blood supply chain. Fractionation alternatives and aphaeresis technologies differ in cost and efficiency. Blood managers are often faced with choosing the technology to be used in the collection and production of blood products. This decision becomes complex since multiple aspects should be taken into account in the decision-making process. The technology selection and collection strategy should consider aspects such as demand structure, compatibilities, donor availability, blood type proportions, costs, and process efficiencies. On the other hand, the use of a demand forecast is not always enough to make a strategic decision like this; a robust decision must consider uncertainty and possible variations in the demand as well as trade-offs between the different objectives to be studied. To support the technology decision as well as donor assignment, a multi-objective stochastic integer linear programming model is proposed. This model considers the demand parameter as stochastic and includes multiple constraints such as capacity, proportionality, and demand fulfilment. The model seeks to optimize two objectives, the total cost and number of donors required. For this combination of a multi-objective problem and a stochastic problem, we propose a novel combination of Sample Average Approximation and the Augmented Epsilon-Constraint algorithm. The proposed methodology is evaluated using actual information from Bogota, Colombia.

4.1 Introduction

The blood supply chain comprises the processes of collecting, testing, processing and distributing blood and blood products, from donor to recipient. Blood products are transfused to patients as part of routine medical treatments or surgical operations, and also in emergency situations. However, the increasing demand for blood products as well as the decreasing population of donors makes decision-making for the blood supply chain challenging Seifried et al. (2011), and this is particularly the case in developing countries with limited resources. On the other hand, shelf-life constraints, multiple

products, compatibilities and blood proportions make the problem complex, limiting the set of methodologies suitable.

Different configurations of the blood supply chain can be found in developed and developing countries. Developed countries tend to have centralised systems, while, in developing countries, the systems are often more decentralised. For example, in the UK there are five large production centres that supply blood for England and Wales Woodget (2014); in contrast, in Colombia there are 85 production centres of different sizes that provide blood products for the whole country. Another important difference between developed and developing countries is the availability of resources. According to the World Health Organization, the blood donation rate in high-income countries is 36.8 donors per 1000 population, while in middle-income and low-income countries it is 11.7 and 3.9 donations per 1000 population respectively (WHO 2014). Hence, blood supply chain management is challenging in general; however, features such as economic resources, donor behaviour and decentralization of the system have made these kinds of decisions even more challenging in developing countries.

A recent review Osorio et al. (2015) of quantitative models in the blood supply chain identifies several gaps in the literature. One of the gaps identified is the necessity to study the different collection and production alternatives, given that blood products can be obtained in different ways that differ in terms of cost and efficiency. Decisions about strategies to fulfill demand considering whole blood and aphaeresis donations have been rarely studied in general.

This paper contributes in two different ways. Firstly, the model proposed in this paper includes several characteristics that have not been taken into account in previous research in quantitative models for the blood supply chain, for example, the combination of uncertainty and multiple objectives simultaneously. Furthermore, the model includes other aspects that are rarely considered in blood supply chain literature such as multiple collection methods and multiple products simultaneously. Given a stochastic annual demand for blood products, the model supports strategic decisions such as technology selection and donor allocation and the use of substitute products in order to meet demand while minimising both cost and the number of donors required. Secondly, in order to deal

with uncertainty and multiple objectives, this work proposes a novel methodology that integrates two other approaches, namely Sample Average Approximation (SAA) and the Augmented Epsilon-Constraint algorithm. The model and the proposed methodology are evaluated using actual data in the public domain from Bogota, Colombia INS (2013).

The structure of this paper proceeds as follows: Section 4.2 presents the literature review of the main concepts used in this paper. Section 4.3 describes the problem and the type of decisions to be studied while Section 4.4 presents the general framework of the proposed methodology. Section 4.5 introduces the mathematical formulation of the problem studied. Section 4.6 and Section 4.7 present the conversion of the model into the formulations of the Augmented Epsilon-Constraint algorithm and SAA respectively. In Section 4.8, the integration of the aforementioned methodologies is explained. Finally, in Section 4.9, the results of the application of the proposed model and methodology to a case study are presented, while Section 4.10 presents the main conclusions and extensions of this work.

4.2 Literature Review

4.2.1 Quantitative Techniques Applied in the Blood Supply Chain

Research on the blood supply chain has been focused mainly on finding optimal inventory policies. Examples of this can be found in Pierskalla & Roach (1972), Cohen (1976), Nahmias & Pierskalla (1976), Chazan & Gal (1977) and Jagannathan & Sen (1991). An approach often used is simulation, which usually does not provide optimal solutions, but realistic policies and complex relationships can be studied using this technique. Examples of applications of simulation to the blood supply chain are provided by Rytilä & Spens (2006), Katsaliaki & Brailsford (2007), Baesler et al. (2011, 2014) and Simonetti et al. (2014).

One of the first papers on collection and production was presented by Cumming et al. (1976). In this work, forecasting models to improve collection goals and avoid over-collection were developed. On the other hand, survival analysis is used by Melnyk et al.

(1995) to classify donors. Glynn et al. (2003) and Sonmezoglu et al. (2005) evaluate quality indicators for blood collected during disaster periods. Boppana & Chalasani (2007) develop Markov chains to define optimal collection policies during emergencies.Madden et al. (2007) compare efficiency indicators using both red blood cells obtained by fractionation and red blood cells obtained from the aphaeresis process. Lowalekar & Ravichandran (2010) develop a simulation model to evaluate several collection policies. In Arciniegas & Mosquera (2012) demand forecasts and a deterministic LP model are proposed to assign donors to collection processes over a period of 5 days. However, capacity and uncertainty are not considered. Alfonso et al. (2012, 2013) present two recent studies on this topic: capacity processing and staff required were estimated using Petri Nets and discrete event simulation. In Osorio et al. (2014) a deterministic model to define the collection strategy is proposed. The model presented in the current paper contains some similarities with the models presented in Osorio et al. (2014) and Arciniegas & Mosquera (2012). However, the main difference is that the model presented here considers uncertainty and stockouts as well as the solution methodology developed. In general terms, unlike most of the literature described, this paper consider aspects of the blood supply chain such as uncertainty in demand, multiple collection methods, multiple products and multiple objectives.

4.2.2 Multi-objective Optimization: the Augmented Epsilon-Constraint Algorithm

Several multi-objective optimization techniques have been proposed, such as weighted average methods, goal programming, ε-constraint and metaheuristics; a review of the main methods and applications can be found in Marler & Arora (2004) and Zhou, Qu, Li, Zhao, Suganthan & Zhang (2011). The solution methodology depends on several factors including the complexity of the problem, the solution time and the accuracy level of the solutions. However, in general terms, the aim of multi-objective optimization is to find a set of efficient solutions called the Pareto front. The Pareto front allows the decision-maker to have a wide overview of the behaviour and trade-offs of the different objective functions.

One of the most frequently used methods for finding the Pareto front is the ε-constraint algorithm first proposed by Haimes et al. (1971). The success of the method is based on the simplicity of the idea. This method converts multi-objective problems into mono-objective problems by setting the objective functions as constraints bounded by epsilon parameters. The epsilon parameters are varied, thus obtaining the Pareto front. Examples of applications of this algorithm can be found in Bérubé et al. (2009) and Du et al. (2014). Improvements to the original method have been proposed in Ehrgott & Ruzika (2008) and Mavrotas (2009); in particular, the Mavrotas version is called the augmented ε-constraint algorithm and it is the version used in this paper. The application of the algorithm to the presented problem is explained in detail in Section 4.7.

4.2.3 Sample Average Approximation

Sample average approximation (SAA) is one of the most widely used methods to deal with stochastic programming. In general, the expected value of the optimal solution for the stochastic problem is approximated using the average of samples obtained from probability distributions. According to Kleywegt et al. (2002), this method is designed for problems with three features. Firstly, the expected valued function cannot be easily calculated by analytical methods. Secondly, the value of the objective function can be easily calculated for an instance of the problem with stochastic elements. Finally, the set of feasible solutions is finite but considerably large, making enumeration approaches infeasible. The model presented in this article meets these three features. Theoretical developments of the algorithm such as convergence rates can be found in Kleywegt et al. (2002). Applications can be found in Verweij et al. (2003) and Li (2014), including implementation aspects. Other applications in supply chains can be found in Santoso et al. (2005), Kiya & Davoudpour (2012), Schütz et al. (2009) and Toro-Diaz & Osorio-Muriel (n.d.). Finally, applications in the blood supply chain can be found in Duan & Liao (2013, 2014) and Hemmelmayr et al. (2010). Moreover, in the current paper the application of the SAA algorithm is combined with the multi-objective technique augmented ε-constraint algorithm in order to study the trade-off between multiple objectives in a

stochastic optimization problem. A detailed explanation of the algorithm is presented in Section 4.8.

4.2.4 Combined Multi-objective Stochastic Optimization

Efficient methodologies have been proposed to solve multi-objective problems and stochastic problems independently. However, according to Gutjahr (2016), the combination of multi-objective stochastic problems has not been widely studied. In Gutjahr (2016) a survey of the main types of problems, methods and applications is presented. Literature regarding two-stage multi-objective stochastic optimization is scarce. In Fonseca et al. (2010) the objectives are combined in a single objective function and a set of scenarios is defined a priori. Cardona-Valdés et al. (2011) use the ε-constraint algorithm combined with the L-shaped method (also known as Bender's decomposition) to solve the problem using a set of scenarios also defined a priori. Finally, Tricoire et al. (2012) present a combination of the ε-constraint algorithm with a sampled-based method using a fixed random sample of the stochastic parameters; however, indicators of convergence are not evaluated. The methodology proposed in this paper differs from the aforementioned papers in two main respects; firstly we use the augmented ε-constraint algorithm which is an improved version. Secondly, we use the sample average approximation algorithm to deal with the stochastic problem. This algorithm is sample-based and the solution is not only based on one sample of size N but M samples of size N. This decreases the risk of omitting important scenarios.

4.3 Problem Description

The most common blood collection method, called whole blood donation, consists in extracting approximately 450 cm3 of blood using a set of collection bags. The blood is centrifuged and, depending on the velocities and times, different components can be obtained using fractionation. The four main components derived from whole blood are red blood cells (RBCs), platelets, cryoprecipitate and plasma. On the other hand, aphaeresis processes, which directly withdraw a single blood component from a donor,

are considerably more efficient than fractionation. For example, two units of red blood cells can be obtained from a donor using aphaeresis, while using fractionation processes only one unit can be obtained. However, this kind of process also has disadvantages. Firstly, it is considerably more expensive than fractionation and the donor time during this process is also longer. Secondly, donors must meet special conditions in terms of weight and haemoglobin levels in order to be able to donate in the case of RBCs by aphaeresis. Finally, only one product can be obtained from aphaeresis, which, depending on the structure of the demand, is not necessarily convenient.

In Colombia, for example, there is no common policy on collection processes, which implies that every region collects blood and blood products according to empirical decision rules. For example, in the Valle del Cauca region in 2012, 93% of platelets were collected using aphaeresis processes while in the same period in the Antioquia region this percentage was just 42%. However, most regions collect platelets from whole blood donations. In the case of RBCs, the greatest proportion of RBCs produced using aphaeresis processes is in the Tolima region with 8.24%, followed by 6.26% from Bogota. Again, most regions obtain RBCs exclusively from whole blood donations.

Table 4.1 shows the five most common processes and the quantities of products obtained by assigning one donor to each process. The quantities are represented in standard transfusion units. According to Table 4.1, one unit of whole blood collected in a triple bag yields one unit of RBCs and one unit of plasma. For quadruple bags, there are two fractionation alternatives: Alternative A generates one unit of RBCs, one unit of plasma and one unit of platelets, whereas Alternative B produces one unit of RBCs and one unit of cryoprecipitate.

Table 4.1: Blood products obtained in each process.

Process	**RBCs**	**Plasma**	**Platelets**	**Cryoprecipitate**
Triplex bag	1	1		
Quadruple bag – Alternative A	1	1	1	
Quadruple bag – Alternative B	1			1
RBC by apheresis	2			
Platelets by apheresis			10	

A special feature of the blood supply chain is the possibility of using substitute products. Compatibility differs depending on the product to be transfused. It is important to highlight that transfusion compatibilities can be defined by several factors such as the preferences of physicians, specification of medical treatments and availability. The compatibility relationships used in this paper are presented in Appendix C.1.

The model proposed in this paper is aimed at finding optimal relationships between the number of donors required and cost. Given uncertain demand, the model seeks the set of solutions that optimizes both cost and the number of donors required. The case study presented in this article is developed using actual data on demand for blood products during one year in Bogota, Colombia. Costs information is based on the legal product list cost of the same country as well as commercial prices of the equipment. The probability distributions for yearly demand are assumed to be triangular since there is not enough information available to apply statistical procedures to fit a probability distribution.

4.4 Methodology

In order to solve the problem presented in this work, we propose an integrated methodology based on a combination of the SAA method and the augmented ε-constraint algorithm. The general idea is to solve one SAA problem for each epsilon value. The Pareto front generated is composed of the assigned value of one objective and the expected value of the other objective. The steps of the methodology proposed are described in Figure 4.1.

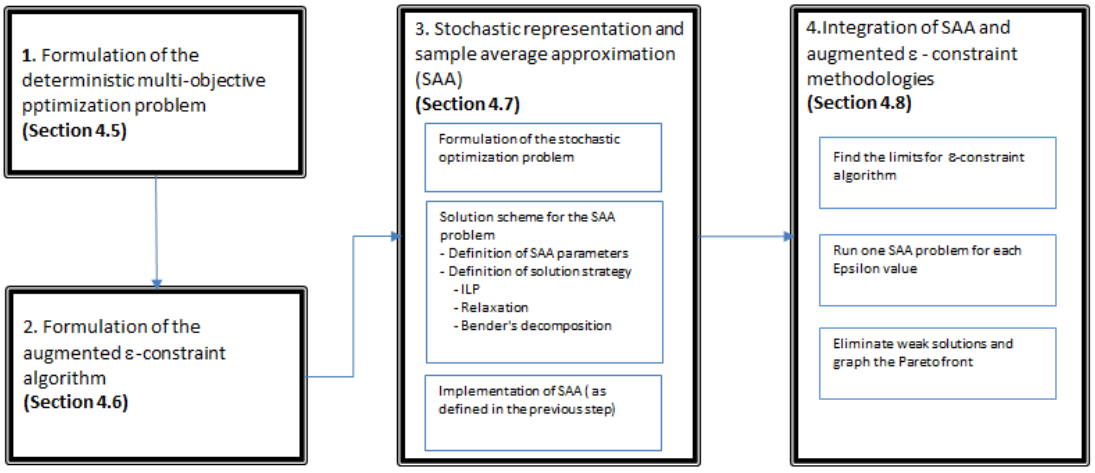


Figure 4.1: Methodology to solve the multi-objective stochastic optimization problem .

The first step of the methodology, presented in Figure 4.1, is the formulation of the multi-objective optimization model (developed in Section 5). This means the explicit representation of the objective functions as well as the set of constraints. In Step 2, described in Section 6, the model formulated is converted into a mono-objective optimization model using the augmented ε-constraint methodology. The main purpose is to define one objective function and set the remaining objective functions as constraints. In Step 3, the new formulation of the model is converted into a stochastic model by introducing the uncertain parameters. In this section, the model is also formulated as a two-stage optimization model. The methodology to deal with the stochastic model is the SAA algorithm; however, experimentation is required in order to define the SAA parameters and the solution methodology for the SAA problem. Once a solution strategy and a set of acceptable parameters have been chosen, Step 4 aims at finding the Pareto front of the problem. In order to find efficient solutions, Step 4 applies the augmented ε-constraint algorithm, solving one SAA problem for each epsilon value. Finally, weak solutions are discarded and the Pareto front can be drawn.

4.5 Formulation of the Multi-Objective Optimization Model

The integer linear programming model described in this section optimizes two objective functions which are conflicting(as discussed in Section 4.5.2). On the one hand, total production costs are minimised. On the other hand, the number of donors is also minimised. Different features of the blood supply chain are considered, such as proportionality of blood groups, multiple products, use of compatible products and different collection methods. These features are modelled as constraints or included in the definition of the decision variables.

This model can be seen as a two-stage optimization model since it considers first- and second-level decisions. The first-level decisions are tactical and are related to the number and type of collection equipment to be acquired. These decisions must be made at the beginning of the planning horizon before demand has occurred. Since demand is a stochastic parameter, the challenge is to make good first-level decisions that consider the stochastic nature of the problem. Second-level decisions are made once demand is known. In the case of the blood supply chain, these decisions define the number of donors required and the strategy associated with collection and the use of substitute products.

4.5.1 Integer Linear Programming Model

Definition of Sets

I	=	Blood types – indexed by i.
K	=	Collection alternatives – indexed by k.
J	=	Products required – indexed by j.
E	=	Available Technologies – indexed by e.

Model Data (Information Provided)

A_{ijk}	=	Number of units of product type j obtained from applying process k to a unit of blood type i, $i \in I$, $j \in J$, $k \in K$.

P_k = Collection cost for one donor assigned to collection method k, $k \in K$ [US$].

F_e = Fixed cost of purchasing one unit of equipment of technology e, $e \in E$[US$].

C_e = Processing capacity of a unit of equipment of technology e, $e \in E$[US$].

R_{ke} = Amount of resource type e required for collecting from a donor by process type k, $e \in E$, $k \in K$. [mins]

D_l = Predicted demand for product l, $l \in J$, [Units of product].

H_l = Penalty cost for a stockout of product l, $l \in J$, [US$].

O_{jl} = = 1 if product j is substitutable with product l, 0 otherwise, j and $k \in K$.

N_i = Proportion of blood type i in the population studied, $i \in I$.

α_j = Historical discard rate of product j, $j \in J$.

B = Proportion of eligible population for RBCs aphaeresis

Decision Variables

x_{ik} = Required number of donors of blood type i, for collection using process k, $i \in I$, $k \in K$.

z_{jl} = Quantity of product type l that will be supplied by substitute product type j, $j, l \in J$.

y_e = Quantity required of equipment of technology e, $e \in E$.

Auxiliary Variables

s_l = Estimated stockout of product l in period t, $l \in J$ [Units].

Objective Function

$$\min F_1 = \sum_{i\in I}\sum_{k\in K} P_k x_{ik} + \sum_{e\in E} F_e y_e + \sum_{l\in J} H_l s_l \tag{4.1}$$

$$\min F_2 = \sum_{i\in I}\sum_{k\in K} x_{ik} \tag{4.2}$$

Constraints

$$\sum_{j\in J} z_{jl} O_{jl} + s_l \geq D_l(1+\alpha_l), \quad \forall l \in J \tag{4.3}$$

$$\sum_{l\in J} z_{jl} \leq \sum_{i\in I}\sum_{k\in K} x_{ik} A_{ijk}, \quad \forall j \in J \tag{4.4}$$

$$\sum_{k\in K} x_{ik} \leq N_i \sum_{a\in I}\sum_{k\in K} x_{ak}, \quad \forall i \in I \tag{4.5}$$

$$\sum_{i\in I}\sum_{k\in K} x_{ik} R_{ke} \leq C_e y_e, \quad \forall e \in E \tag{4.6}$$

$$x_{i4} \leq \sum_{k\in K} x_{ik} B, \quad \forall i \in I \tag{4.7}$$

$$x_{ik},\ z_{jl},\ y_e, \in \mathbb{Z}^+ \tag{4.8}$$

Equation (4.1) represents the annual cost of meeting the demand for blood products including variable and fixed costs. On the other hand, the second objective function (4.2) computes the total number of donors required to meet the demand, considering all blood types and processes. Constraints (4.3) guarantee satisfaction of the demand (increased by the discard rate) for each product, and constraints (4.4) define the quantity of product available as a function of the number of donors. Constraints (4.5) ensure that the proportionalities of each blood type of the population studied are conserved in the solutions of the model. Capacity constraints (4.6) define the availability of each resource according to the number of units of equipment for each technology. Finally, constraints (4.7) limit the number of donors that can be assigned to the process of producing RBCs by aphaeresis.

4.5.2 Multi-objective Nature of the Problem

The model proposed contains two objectives that conflict: $F_1(x)$ refers to the total cost, while $F_2(x)$ represents the number of donors required. The competition between objectives arises because there are several alternatives of donor allocation that differ in terms of cost and the quantity of products obtained. For example, considering a particular realization of the random vector of demand (using the mode value), the cost function takes a value of \$23.33m when it is minimised, and the number of donors required for this case is 165,729. On the other hand, for the same realization the cost function takes a value of \$30.36m when the number of donors is minimized, achieving a minimum value of 137,352 donors. The ranges for each objective function are given in Table 4.2. Given this situation, it is necessary try to find trade-offs between the objectives. Table 4.2 presents the values for both objective functions given three cases: low, mode and high values of a triangular distribution used to model demand for blood products.

Table 4.2: Extreme limits for each objective function.

Scenario	Objective Function	Total Cost	Number of donors
Low	Minimise cost	22.18	157,466
	Minimise number of donors	22.88	130,483
Mode	Minimise cost	23.33	165,729
	Minimise number of donors	30.36	137,352
High	Minimise cost	26.84	190,600
	Minimise number of donors	34.85	157,951

As can be observed, the extreme lower and upper limits for the cost are \$22.18m and \$34.85m respectively. On the other hand, the limits for the donor function are 130,483 and 190,600. These values were calculated by solving the problem in a lexicographic way. This means that to calculate the maximum value for one objective we set the other objective as a constraint limited by the minimum value. The aforementioned limits are calculated only for the deterministic problem considering specific values of the probability distribution. However, the general limits for the objective functions in the stochastic multi-objective problem cannot be defined directly.

4.6 Formulation of the Augmented Epsilon-Constraint Algorithm

The ε-constraint technique proposed in Haimes et al. (1971) consists of converting a multi-objective problem into a mono-objective problem. To do this, the decision-maker must pick one objective function to remain as the objective and set the others as constraints bounded by a set of parameters called epsilons. These parameters are defined specially for each objective converted into a constraint. In order to generate the Pareto front, the algorithm solves one mono-objective optimization problem for each value of the epsilon parameters and repeats this process for multiple values of the epsilon parameters. Typically, the values of the epsilon parameters are given by a systematic variation inside an interval. However, this form of the algorithm usually generates weak solutions, since the objective value could not be improved for some subsequent epsilon values. In order to try to avoid this, and accelerate the whole process, Mavrotas (2009) proposed an improved version called the augmented ε-constraint algorithm (described in Appendix C.2). The formulation presented in Appendix C.2 is general and considers k objective functions; however, our model contains only two objective functions. Hence, the normalization parameter r (described in Appendix C.2) is not included. The number of solved models depends on how many epsilon values the decision-maker wants to analyse. As the increment of epsilon becomes smaller, the algorithm will probably present a more detailed representation of the Pareto front but the computational cost will also be larger. Additional details of the algorithm can be found in Mavrotas (2009).

In order to apply the augmented ε-constraint algorithm as the solution methodology to the problem presented in Section 4.5, two main modifications are introduced to the model. Firstly, the objective function minimising total costs is adapted by including the new surplus variable w as well as its coefficient β; the value of the coefficient β is assumed to be -10^{-5} and it is taken by reference from Mavrotas (2009). The formulation is presented as follows:

$$\min F_1 = \sum_{i \in I} \sum_{k \in K} P_k x_{ik} + \sum_{e \in E} F_e y_e + \sum_{l \in J} H_l s_l - \beta w \tag{4.9}$$

Secondly, the following constraint is added to the model, thus assigning a value to the number of donors objective ($F_2(x)$):

$$\sum_{i \in I} \sum_{k \in K} x_{ik} + w = \varepsilon \tag{4.10}$$

For ease of comprehension, we present the model including these modifications in matrix notation as follows:

$$\min_{x,s,y,w} q^T x + h^T s + c^T y - \beta^T w \tag{4.11}$$

subject to:

$$\boldsymbol{E}z + s \geq d, \tag{4.12}$$

$$\boldsymbol{G}z \leq \boldsymbol{H}x, \tag{4.13}$$

$$\boldsymbol{N}x \leq 0, \tag{4.14}$$

$$\boldsymbol{R}x \leq \boldsymbol{M}y, \tag{4.15}$$

$$\boldsymbol{B}x \leq 0, \tag{4.16}$$

$$\boldsymbol{A}x + w = \varepsilon, \tag{4.17}$$

$$x \in \mathbb{Z}_+^{|I| \times |K|}, z \in \mathbb{Z}_+^{|J|^2}, y \in \mathbb{Z}_+^{|E|} \tag{4.18}$$

Equation (4.11) corresponds to the matrix representation of equation (4.9). In the same way, equations (4.12) – (4.16) are expressions for equations (4.3) – (4.7) respectively, while equation (4.10) is represented in matrix notation by equation (4.17).

In the problem (4.11) – (4.18) vectors q, c, d and h correspond to the production cost, fixed cost, and demand and stockouts penalty respectively. The symbol ε corresponds to a scalar value that represents the maximum number of donors. The matrix E represents the compatibility coefficients in constraints ((4.3). $\boldsymbol{G}$, $\boldsymbol{N}$, $\boldsymbol{B}$ and $\boldsymbol{A}$ represent the summations on the left-hand side of expressions (4.4), (4.5), (4.7) and (4.10) respectively.

Finally, matrices $\boldsymbol{H}$ correspond to the coefficients of the production efficiency in equation (4.4), while $\boldsymbol{R}$ and $\boldsymbol{M}$ represent the resource consumption and capacity respectively in equation (4.6).

In addition, x, z, w and s are vectors for decision variables. Variable x allocates donors to processes while z refers to the use of substitute products. Variable w is the surplus variable of the augmented ε-constraint formulation, while variable s corresponds to the number of stockouts. q is a cost vector associated with the variables in x. Constraints (4.12) – (4.18) refer to demand satisfaction, availability of products and proportionality, which are dominated by the type and quantity of equipment used associated.

4.7 Stochastic Representation and Sample Average Approximation (SAA)

4.7.1 Treatment of the Stochastic Nature of the Problem

Uncertainty in the blood supply chain is mainly related to two sources, demand for products and donor arrivals. Demand for products depends on multiple factors such as surgeries, clinical treatments, emergencies and disasters. On the other hand, donation is a voluntary process that depends mainly on altruistic motivation. The deterministic model presented in Section 4.5.1 is aimed at determining the capacity needed for each type of technology as well as the number of donors required. In the following models, we treat the uncertainty of the sources in different ways. Firstly, the uncertainty associated with demand for products is included as a stochastic parameter in the optimization model, as described in Section 4.7. Secondly, since the aim of the model is to define the number of donors required from a strategic point of view, the uncertainty in donations is represented by an upper limit corresponding to the realized number of donors in the data analysed. In other words, the epsilon values will always be lower than the feasible number of donors for the analysed period.

4.7.2 Formulation of the Stochastic Optimization Problem

The nature of the problem indicates that decisions on collection technology need to be made in advance, this is before the realization of the demand. The number of collections required is determined by the demand after the uncertainty has been revealed. Given this the problem can be stated as a two-stage stochastic linear model with recourse, where the decision on number of pieces of equipment needed to collect and process blood must be made before any realization of demand. The optimization problem seeks then to support the decisions of the first stage based on the expected value of the second stage. The first stage of the problem can be formulated as follows:

$$\min_{y} f(y) = c^T y + E[Q(y, \xi)] \tag{4.19}$$

subject to:

$$y \in \mathbb{Z}_{+}^{|E|} \tag{4.20}$$

In this notation, c represents a cost vector related to first-stage decisions. In the specific case of the model presented in this article, these decisions are related to the quantity of equipment for each technology to be used. The term y is then a vector of integer variables. $|E|$ relates to the problem size, in other words, how many first-level decisions are optimised. The term $Q(y, \xi)$ refers to the optimal value of the following optimization problem (second stage:

$$Q(y, \xi) = \min_{x,z,s,w} q^T x + h^T s - \beta^T w \tag{4.21}$$

subject to constraints (4.13) – (4.18) and to:

$$\boldsymbol{E}z + s \geq d(\xi). \tag{4.22}$$

In constraint (4.22), ξ represents a random vector associated with the stochastic nature of the demand. The optimal value for the problem (4.13) – (4.18), (4.21) and (4.22) is a function of the first level variables y, and a particular realization of the random

vector ξ. The second stage, represents decisions that can be modified according to demand realization. This decisions are number of donors required by blood groups and collection method represented by the vector x and the strategy in the use of substitute products represented by the vector z. These decisions are made after the uncertainty of demand has been revealed.

The probability distribution function for the random vector is assumed to be known so that the expected value can be obtained. Using a sampling average approach, the expected value $E[Q(y,\xi)]$ can be calculated taking the average of the individual values of the samples of size N. In the particular context of this work the resulting model is integer and linear. The problem can be re-stated as follows:

$$\min_{y}\{\hat{f}_N(y) = c^T y + \frac{1}{N}\sum_{n=1}^{N} Q(y,\xi^n)\} \tag{4.23}$$

The SAA method proposes a methodology to deal with the uncertainty using sampling. The logic of the algorithm is simple, generating samples of the random vector ξ and solving one deterministic model for each realization of the samples generated. The algorithm also allows evaluation of the convergence for different sample sizes, in terms of an estimated optimality gap and its variance. The complete methodology to solve the problem presented in equation (4.23) is described in Appendix C.3.

4.7.3 Solution Strategy for the SAA Problem

The solution of the SAA problem presented in equation (4.23) can be challenging, depending on the nature of the variables and the size of the problem. Given that the solution approach of the multi-objective problem implies the solution of multiple SAA problems, the solution time for every SAA problem is a very important aspect. In order to find an acceptable solution of the SAA problem in a short time, three different approaches are studied. First, the problem is solved considering N scenarios simultaneously, keeping the integrality condition over all the variables. This approach corresponds to configurations 1–3 in Table 4.3. The second approach also considers N scenarios simultaneously; however, in this case the integrality constraints for some of the decision

variables are relaxed: in configuration 4–6, only the variables w and s are allowed to be continuous, while in configurations 7–9 relaxation is applied to the integrality constraints for all variables with the exception of first-stage variables y.

Unlike the other two approaches, the third approach solves the problem using decomposition instead of simultaneity. This approach consists in the application of Bender's decomposition algorithm (also known as the L-shaped method) to solve the SAA problem (see Appendix C.4). The results of the application of this approach are presented in configurations 10–12. According to the results obtained in Table 4.4, in terms of convergence, solution time and the size of the samples, configuration number 9 is chosen to run the combination of the augmented ε-constraint algorithm and SAA. This configuration performed well for this specific problem; however, the strategy for solution of the SAA problem could require the application of acceleration techniques for Bender's decomposition, or other optimization techniques such as branch and price or branch and cut.

4.7.4 Implementation of SAA

For the solution of the models, the problems were coded using the Gurobi Java Interface and solved using Gurobi solver version 5.3.6. The SAA and augmented ε-constraint procedures were also implemented using Java as the language for controlling the algorithm. The computational experiments were performed in a PC running Windows 7, with 4 GB of RAM memory and an i5 processor. The values obtained for the objective function and convergence indicators are presented in Table 4.4. The size of the samples and the number of samples for the SAA are taken by reference to other works, such as Verweij et al. (2003) and Santoso et al. (2005). The gap estimator for all cases is lower than 1%, which is a good indicator of convergence of the algorithm and suggests acceptance of the validity of the parameters chosen.

Table 4.3: Summary of model features for different configurations of the SAA problem (see Appendix C for the explanation of N, M and N').

Configuration	N	M	N'	Methodology	Variables with integrality constraints relaxed	Variables with integrality constraints	Continuous variables	Integer variables SAA problem	Number of constraints SAA problem	Total number of models solved	Time (sec.)
1	20	10	500	Simultaneously	-	y, x, z, w and s	0	9223	1200	510	118
2	40	10	500	Simultaneously	-	y, x, z, w and s	0	18443	2400	510	340
3	30	20	1000	Simultaneously	-	y, x, z, w and s	0	13833	1800	1020	343
4	20	10	500	Simultaneously	w,s	y,x and z	420	8803	1200	510	112
5	40	10	500	Simultaneously	w,s	y,x and z	840	17603	2400	510	156
6	30	20	1000	Simultaneously	w,s	y,x and z	630	13203	1800	1020	239
7	20	10	500	Simultaneously	w,s,x,z	y	9220	3	1200	510	11
8	40	10	500	Simultaneously	w,s,x,z	y	18440	3	2400	510	15
9	30	20	1000	Simultaneously	w,s,x,z	y	13830	3	1800	1020	22
10	20	10	500	Decomposition	w,s,x,z	y	9220	3	1200	510	28
11	40	10	500	Decomposition	w,s,x,z	y	18440	3	2400	510	58
12	30	20	1000	Decomposition	w,s,x,z	y	13830	3	1800	1020	76

Table 4.4: Summary of SAA results for different sample sizes using cost as objective function (see Appendix C for the explanation of the SAA estimators).

Configuration	N	M	N'	Methodology	Variables with integrality constraints relaxed	Variables with integrality constraints	$\bar{v}_{N,M}$	$\sigma^2_{\bar{v}_{N,M}}$	$\tilde{f}_{N'}(\bar{y})$	$\sigma^2_{N'}(\bar{y})$	$gap_{N,M,N'}$	σ^2_{gap}
1	20	10	500	Simultaneously	-	y, x, z, w and s	29.34	0.035	29.561	0.00606	0.0074	0.042
2	40	10	500	Simultaneously	-	y, x, z, w and s	29.46	0.0041	29.66	0.0118	0.0067	0.016
3	30	20	1000	Simultaneously	-	y, x, z, w and s	29.47	0.0087	29.716	0.0104	0.0082	0.0192
4	20	10	500	Simultaneously	w,s	y,x and z	29.41	0.02	29.5485	0.004	0.0005	0.024
5	40	10	500	Simultaneously	w,s	y,x and z	29.46	0.0086	29.693	0.0044	0.0076	0.0131
6	30	20	1000	Simultaneously	w,s	y,x and z	29.46	0.0057	29.681	0.0022	0.0073	0.008
7	20	10	500	Simultaneously	w,s,x,z	y	29.24	0.0118	29.422	0.0064	0.0059	0.0182
8	40	10	500	Simultaneously	w,s,x,z	y	29.41	0.0246	29.5395	0.004	0.0043	0.0287
9	30	20	1000	Simultaneously	w,s,x,z	y	29.41	0.023	29.5743	0.0023	0.0055	0.0253
10	20	10	500	Decomposition	w,s,x,z	y	29.23	0.0185	29.5163	0.0213	0.0094	0.0398
11	40	10	500	Decomposition	w,s,x,z	y	29.28	0.011	29.4187	0.0044	0.0046	0.0154
12	30	20	1000	Decomposition	w,s,x,z	y	29.29	0.0037	29.4183	0.00594	0.0043	0.0097

4.8 Integration of SAA and Epsilon-Constraint Methodologies

The integrated methodology proposed requires some experimentation to define the limits of the ε-constraint algorithm. The traditional approach would generate many infeasible models for some epsilon values or, in this case, models with a large number of stockouts, since the model has been modified to avoid infeasibility.

Given the stochastic nature of the problem, the limits of the ε-constraint cannot be defined directly by the lexicographic solution of the deterministic model. It is necessary to do experimentation in order to define an acceptable starting lower boundary for the augmented ε-constraint algorithm. The lower boundary will depend on the number of stockouts allowed. Once an acceptable lower level has been defined, the augmented ε-constraint algorithm can be run over the interval composed by the lower limit calculated and the maximum value of donors described in Table 4.2. In the case of the model defined, the lower limit found is 148,000 donors and the upper limit is 190,600 donors. Another approach can be building the Pareto front by intervals, switching between the objective functions at some point of the Pareto front. In this case, the solution defines the limits implicitly.

The disadvantage of the integrated methodology can be the computational time, since for each value of epsilon an SAA model must be run. For example, running 100 epsilon values and a SAA model with parameters N, M and N' (described in Appendix C) equal to 30, 20 and 1,000 respectively (see configuration 9 in Tables 4.3 and 4.4), which would generate 102,000 deterministic, mono-objective models. The number of models will depend on the convergence of the stochastic problem and the level of accuracy in the Pareto front accepted. This approach can work and generate robust decision support but it depends on the solution time of the SAA problem. If this time is too long, the execution time of the complete methodology can be prohibitive. Table 4.5 presents the parameters for executing the integrated methodology.

In Table 4.5, three settings are presented which differ by the number of epsilon values to be evaluated and the results generated. The first setting presents the evaluation of 40

Table 4.5: Parameters configuration and solutions generated for Configuration 9

	Setting 1	Setting 2	Setting 3
SAA solution strategy (see Tables 4.3 and 4.4)	Configuration 9	Configuration 9	Configuration 9
Number of epsilon values	40	60	100
Models solved	40800	61200	102000
Optimal solutions found	25	32	53
Execution time (min)	19.5	32.5	52.1

epsilon values; in this case, the running time is shorter but only 25 optimal solutions are obtained. In contrast, Setting 3 presents the evaluation of 100 epsilon values, increasing the execution time but generating a more accurate representation of the Pareto front.

4.9 Results

The Pareto front presented in Figure 4.2 contains the set of efficient solutions obtained using Setting 3 according to 4.5 and the specific demand structure of the case study. In particular, the decision-maker can analyse the impact of a given maximum budget on the minimum number of donors, or conversely. In the case of any region of interest, the decision-maker can re-set the limits of the algorithm and run it again in order to obtain solutions with more precision. It is important to highlight that final decisions must consider other aspects such as the capacity to motivate donors for the different collection methods and the preferences of physicians for each collection method.

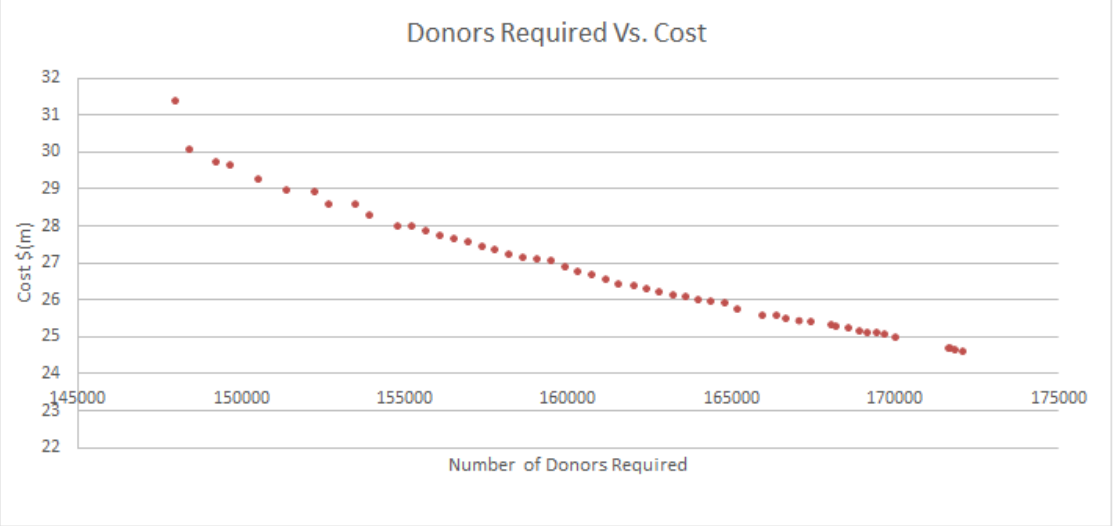


Figure 4.2: Pareto front for multi-objective stochastic model presented.

Another important result is the allocation of donors for the different processes. Since the processes analysed differ in terms of efficiency and cost, the specific allocation of donors to each process will also be affected by constraints in terms of cost or the maximum number of donors required. Figure 4.3 presents the rate of allocation to each process given a budget. The curves are based on the solutions of the stochastic optimization problem including the budget objective constraint.

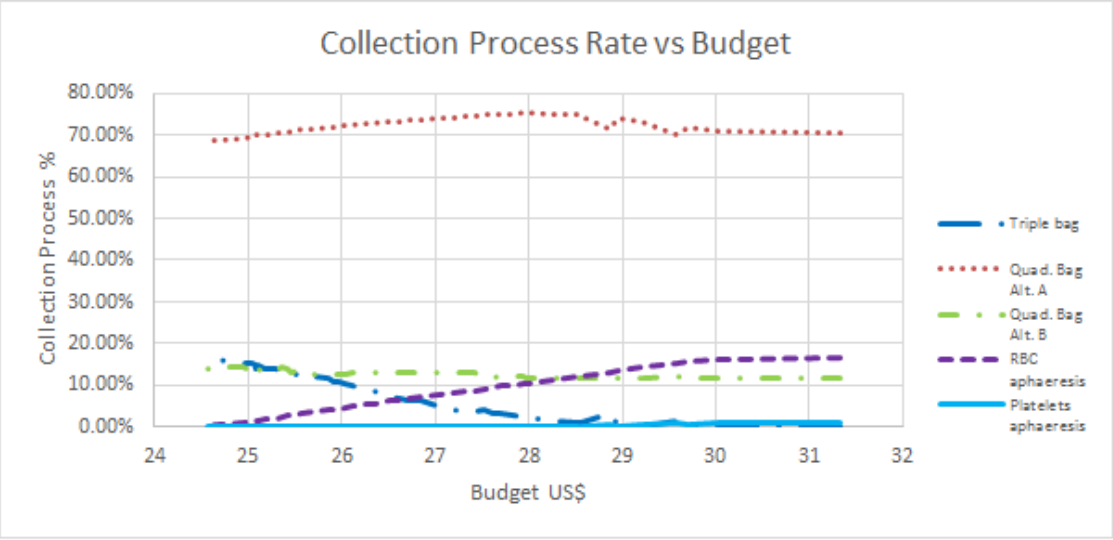


Figure 4.3: Allocation rates for each process.

As expected, the proportion of donors assigned to aphaeresis collection methods increases when the budget is bigger, but this also means that the number of donors required is lower according to the Pareto front. Combining Figure 4.2 and Figure 4.3, the decision-maker can observe the behaviour and donor allocation for each process, when both objectives are optimised.

Finally, once the decision-maker defines a point on the Pareto front to set the operation of the system, additional information can be obtained by using the solutions of particular stochastic optimization problems. At a lower level, details about the allocation for specific blood groups and the use of substitute products can also be obtained.

Table 4.6 and Appendix C.5 present an example of the solution obtained, given, for example, a maximum number of donors of 155,000. Table 4.6 presents the allocation of donors for the different processes by blood type. The solution obtained conserves the proportionality of blood types of the population studied. The results presented in Table 4.6 correspond to the demand structure of this particular case. Other important information obtained from solutions is the use of substitute products: Tables C.4 to C.7 in Appendix C.5 present details about the allocation of each product to meet the demand of other products.

Table 4.6: Donor allocation to each process for a maximum number of donors of 155,000

Process	A-	A+	AB-	AB+	B-	B+	O-	O+	Total
Triple bag	28	783	8	324	4	1382	16	1397	3942
Quadruple bag – Alternative A	3167	31822	378	1326	749	7423	5674	65884	116423
Quadruple bag – Alternative B	428	6472	78	617	162	2046	235	8402	18440
2-RBC (RBC by aphaeresis)	522	1391	8	12	154	427	1983	11589	16086
Platelets by aphaeresis	44	8	13	4	21	11	32	13	146
Total	4189	40476	485	2283	1090	11289	7940	87285	155037

It should be noted that the total number of donors in Table 4.6 is slightly higher than 155,000, which occurred because the decision variables are relaxed. In order to obtain an integer solution, the results have been rounded up and the total number of donors may be higher than the epsilon value of the SAA execution. In this case, the decision-maker

could evaluate the viability of the solution or re-scale the results according to the epsilon value chosen.

4.10 Conclusions and Further Research

Decision-making in uncertain environments is a complex task. The methodology used to generate robust solutions will depend on the features of the models and resources available. The model presented in this paper considers demand as a stochastic parameter. Since the model introduced is linear and its deterministic version is easy to solve using an optimization package, the SAA methodology combined with the augmented ε-constraint have been used. This methodology facilitates obtaining a robust solution that considers the stochastic nature of the demand. The solution obtained also guarantees that features such as proportionality and compatibility are met.

The blood supply chain has been widely studied, but previous studies have focused mainly on the development of inventory policies. However, this study is aimed at studying decision stages such as collection and production, which have received less attention. Another important aspect of this research is that it considers multiple products, instead of focusing on individual products, since fractionation processes always generate more than one product.

The optimal collection strategy will depend on several factors such as demand structure, preferences, donor response to the different collection methods and budget. However, robust methodologies such as the one demonstrated here support the decision-making processes, presenting a wide view of the impact of choosing one or other strategy. In the particular case of this work, the relationship between the number of donors required and cost is presented. In addition, making optimal decisions considering all the blood supply chain aspects such as compatibilities and proportionalities is almost impossible without using advanced decision-making methodologies.

The proposed model can be used by blood centres to plan the collection strategy; the information used in the model is usually readily available in blood centre information

systems. The model assumes the use of substitute products, but this can be easily modified by changing the compatibility parameter. Finally, the model has been solved used the Gurobi solver; however, other efficient solvers are available and can be integrated into spreadsheets to facilitate their implementation and use. A similar version of the proposed model was modelled in Excel and solved using Open Solver. In that case, the model was tested using data from one of the largest blood centres in Colombia in order to obtain the annual plans.

There are multiple extensions of the presented model that can be studied. We have included the most common products and processes; however, there are other products such as irradiated or washed products that can be considered. There are also other alternatives of assignment or fractionation; an example of this is whole blood or plasma aphaeresis. Another possible extension is the inclusion of purchase decisions, depending on whether the systems allow purchasing from external entities. In that case, it would be interesting to study the best way to supply demand, including internal and external sources. In addition, the inclusion of preferences on compatibilities can also be modelled. Finally, another possible adaptation is the inclusion of different types of demand and preferences to meet them.

Chapter 5

Designing the Blood Supply Chain: How much, How and Where?

Abstract

BACKGROUND: Different configurations of the blood supply chain can be found all over the world. The design of the network depends on factors such as geography, politics, costs, and service level; however, most developed countries have moved to centralized facilities, such as large scale production centers. This centralization has also involved the creation of distribution centers, to maintain service levels and to meet distance and time constraints. However, the goal remains the same, satisfying demand for blood products at minimal cost and with minimal wastage.

STUDY DESIGN AND METHODS: Blood supply system design can be viewed as a mathematical location-allocation problem. Most of the location-allocation models in the blood supply chain modeling literature have not considered important aspects of the problem such as alternative methods of collection and production that might influence the optimal design of the network. In this paper we present a stochastic mixed-integer linear programming model to support decisions such as location, allocation, capacity definition and collection and production strategy.

RESULTS: This approach is illustrated in a case study (Colombia) to design the blood supply chain given different distance covering constraints. For each scenario an optimal configuration is obtained, together with a strategy for collection and production decisions. In addition, our method is used to evaluate the impact of using collection by apheresis in the case study.

CONCLUSION: The selection of a particular configuration depends on many factors. However, centralized systems are more efficient than decentralized systems. Decentralized systems may be preferred for other reasons, such as political or geographical concerns. The proposed model allows the network to be designed under different travel time constraints.

5.1 Introduction

Demand for blood has undergone significant changes in recent years. Seifried et al. (2011) point out that demand for blood is increasing due to new treatments, while the donor population is decreasing in developed countries because of the ageing population. Whitaker et al. (2016) note that in the US the demand for blood has actually decreased from 2011 to 2013, but collection rates have decreased at a higher rate in the same period. Uncertainty in supply and demand, together with special features of blood products such as short shelf life, make the planning process in the blood supply chain a complex task.

The blood supply chain can be subdivided into four stages: collection, production, inventory and distribution. Collecting blood is an activity that requires enormous effort; donations are usually voluntary and the willingness of individuals to donate depends on many factors such as distance, the level of physical discomfort, and personal motivation. Hence, blood collection centers are typically close to donor populations to facilitate access and encourage donations. However, blood is also perishable and needs to be processed within a certain time period after collection to meet clinical and regulatory guidelines; for example, Colombian regulations state that whole blood must be processed and the components stored at the appropriate temperatures within 8 hours after collection (INS 2011). In addition, different collection methods can be used, which impact the number of products obtained and the costs of collection and production. In terms of production, several different schemes are used around the world. In general, developed countries tend to centralize production processes in large centers, but the level of centralization is lower in developing countries. For example, in the UK there are five large production centers that supply blood for England and Wales (Woodget 2014) for a population of approximately 57.1 million; in contrast, in Colombia there are 82 blood banks of different sizes that provide blood products for a population of approximately 48 million in 2015. Of these 48 million, approximately 75.4% live in the regional capitals and the rest in rural areas (DANE 2011). Furthermore, distribution centers are also common in developed countries, since these centers allow transfusion services to meet

distance and lead time conditions. Stock holding units and/or distribution centers in developing countries usually encompass some, but not all, functions of a blood production center. A multitude of distribution mechanisms can also be found in practice, including private fleets, external partners specialized in transport of this kind of product, public transportation and even commercial transport services. The transportation in the model presented in this paper considers distribution supplied by an external party; decisions about fleet and routes are thus not modeled in the design of the blood supply chain. Given all the aspects mentioned, a key question is raised: what is the optimal network configuration? The answer depends on many factors such as economics, as well as political, geographical and cultural considerations, amongst others. A generic model is proposed in this paper to support decisions on the configuration and design of the blood supply chain, as well as collection and production strategies.

This paper presents a mathematical model to optimize the design of blood supply chains and includes a discussion of the benefits of centralization. To illustrate the approach, a case study is presented using real data for demand and travel times derived from Colombia. Our approach is flexible and enables several aspects such as uncertainty, preferences and alternatives to be modeled and studied.

5.1.1 Background

Two collection methods are currently available in the blood supply chain: whole-blood collection and apheresis collection, both of which use different processes and equipment. Worldwide, most blood products are obtained from whole blood. However, the use of products obtained from apheresis is also frequent in some countries. Whole-blood collection uses phlebotomy and a set of bags to collect approximately 450 ml of blood. The extracted blood unit is then passed to the production stage, where fractionation is performed to obtain the different components. In contrast, apheresis procedures extract whole blood from the donor, but the blood is processed in real time, using equipment that withdraws the desired component (red blood cells, plasma, platelets) and returns the remaining components to the donor. The collection kits to carry out apheresis collection are considerably more expensive than the set of bags for whole-blood donation. However,

using apheresis, several units of the same product can be obtained; for example, two units of red blood cells (RBCs) can be obtained using apheresis. In the case of platelets, the amount obtained by apheresis can help up to three adults or even twelve children. The products obtained from both processes are interchangeable; however, the choice of method depends on the policies and strategies defined by the organization and the operational practices of the staff. Most studies in the literature consider only whole blood donation. However, it is also necessary to consider alternative collection and production methods in terms of efficiency and cost, to define the optimal collection strategy. Production planning can also improve the performance of the indicators of the blood supply chain. The benefits of centralization are well documented in terms of a reduction in inventory and economies of scale. However, production planning can also improve performance indicators such as cost and product availability. Since different collection and production alternatives are available, it is possible to find the optimal combinations of collection and production methods to supply a given demand within a network. Optimal production decisions must consider factors such as the demand for products, donations, blood groups, compatibility, and collection and production alternatives. Table 5.1 presents the most common collection processes.

Table 5.1: Blood products obtained in each process.

No.	Process	RBCs	Plasma	Platelets	Cryoprecipitate
1	Triplex bag	1	1		
2	Quadruple bag – Alt. A	1	1	1	
3	Quadruple bag – Alt. B	1			1
4	RBCs by apheresis	2			
5	Platelets by apheresis			1-2 adult doses*	

*This amount is approximately equivalent to the quantity obtained from 10 units of whole blood

Given the variety of collection and fractionation alternatives, decisions regarding collection should consider not only the number of donors required but also the collection method, the type of bag used and the fractionation strategy. The consideration of the collection method and fractionation strategy improve performance indicators considerably.

5.1.2 Literature Review

Location decisions are typically considered strategic in any supply chain. In the blood supply chain these kinds of decisions are also very important, since the distance between donors, blood centers, and demand points can play an important role in the determination of different performance indicators for the blood supply chain. Or & Pierskalla (1979) present an integrated mathematical model to locate blood centers and allocate hospitals to them to minimize the distance traveled for blood product distribution. The paper includes two algorithms to solve this model. The objective function is only concerned with distance; costs are not considered. Another contribution in location models is presented by Jacobs et al. (1996) who develop an integer linear programming model to evaluate location alternatives and decisions, such as allocation of donors to collection points, allocation of collection points to blood centers and quantities of blood to be collected. The model's main objective is to minimize the distance traveled, while meeting allocation, capacity and demand constraints. Sahin et al. (2007) present two models to support decisions regarding location and allocation in Turkey. The first model minimizes the weighted distance between demand points and blood centers. The second minimizes the number of blood stations according to distance covering constraints. The models are modifications of the well-known pq-median and set covering problems and both are solved using commercial optimization software without any additional solution approach required. Other articles also aimed at locating facilities are presented by Cerveny (1980), Price & Turcotte (1986) and more recently Çetin & Sarul (2009). These articles present heuristics and combined approaches to determine the location of a facility. The main objective is to minimize distance; however, in Price & Turcotte (1986) other criteria such as accessibility and space availability are also considered. Recently, Chaiwuttisak et al. (2016) studied the location of low-cost blood donation and blood distribution rooms for the Thai Red Cross Society. In this paper several objectives, such as distance traveled to the main blood centers, demand-weighted distance and the expected sum of blood donated, are combined in a weighted objective function.

The production stage of the blood supply chain has received comparatively little attention in the modeling literature. A few authors have considered aspects such as production

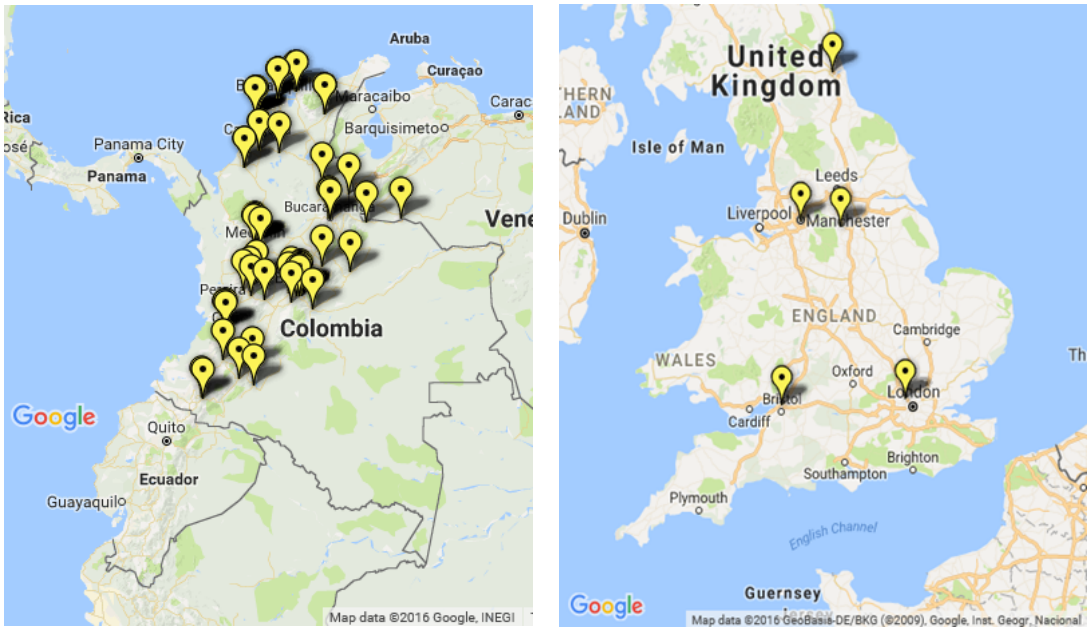
alternatives, single product production and platelet production, as well as production capacity and internal processes. The earliest studies to consider multiple products are presented by Deuermeyer & Pierskalla (1978) and Deuermeyer (1979) who develop an analytical model to minimize the total production costs of RBCs and platelets. Production decisions are associated with different production processes and are defined according to the initial inventories of each product. Some production models have focused exclusively on single products. Sirelson & Brodheim (1991), for example, use simulation to develop profile graphs, where inventory levels are associated with acceptable shortage and outdating rates. Katz et al. (1983) define a platelet production function, based on historical demand and deviations for each day as well as planned inventory and service levels. Ledman & Groh (1984) develop production planning rules considering mean demand, demand variability, and a variety of collection schemes. This paper introduces a number of novel concepts such as collection policies. More recently, special attention has been paid to platelets. Haijema et al. (2007), Haijema et al. (2009) and van Dijk et al. (2009) develop a Markovian model to represent decisions on production and inventories of platelets. Multiple periods, special periods such as weekends and different types of demand are included in the model. Dynamic programming and local search algorithms are used as solution methods, depending on the problem size. Finally, Baesler et al. (2011) present a simulation model to study capacity and support decisions on capacity expansion, in terms of resource utilization and internal waiting times and queues. Most of these studies, however, consider only red blood cells or platelets.

The model proposed in our paper differs in several aspects from the literature: firstly, multiple collection and fractionation methods are considered. Secondly, our model considers four major blood products (RBCs, plasma, platelets, and cryoprecipitate); and thirdly location decisions are made simultaneously with capacity decisions.

This paper is structured as follows. Section 5.2 presents a discussion about the motivations for both centralized and decentralized systems. Section 5.3 describes the mathematical model structure, the solution method used, the case study and the scenarios analyzed. Section 5.4 provides the results and finally Section 5.5 includes discussion of the results and main conclusions of this research.

5.2 Centralization and Decentralization Issues

A key consideration for blood supply networks is a centralized versus a decentralized design. The aim of centralization is to exploit economies of scale. On the other hand, decentralization is mostly employed in cases where geographical or political conditions must be met. Examples of a centralized and a decentralized system are presented in Figure 5.1 where the actual location of blood production centers in the UK and Colombia are represented by yellow icons.



(a) Colombia (200 km Google maps view) (b) England (100 km Google maps view)

Figure 5.1: Location of blood production centers in (a) Colombia and (b) England

5.2.1 Advantages of Centralization

The benefits of centralization in the blood supply chain are well documented in the literature: economies of scale, centralization of inventory, better use of resources, improved consistency and quality control, along with providing a transparent system view that helps managers control and improve key performance indicators. Examples can be found in AuBuchon et al. (2011) and Hosseinifard & Abbasi (2016).

Economies of scale are one of the biggest motivations for centralization in the blood supply chain. The cost of building and maintaining modern blood supply chain infrastructure is high. However when the cost is allocated over the total number of units processed by a facility, economies of scale tend to favor large production centers. An example of this is presented in PAHO (2005) where the cost of a blood unit processed in a large blood center is calculated to be 40% lower than a unit processed in a small blood bank.

Another important aspect favoring centralization is the concurrent reduction in the need for safety stock to deal with variability of demand. With the centralization of blood production centers, there is a requirement for distribution centers to be located closer to the transfusion services. Distribution centers represent an opportunity to reduce safety inventories in the blood supply chain through variance reduction. From elementary inventory theory, it is well known that safety stock should be directly proportional to demand variability. Thus for centers with higher variabilities a large safety stock is required and conversely, in areas with more stable demand, less safety stock is necessary. Chopra & Meindl (2007) demonstrate that the sum of the safety inventory required for several independent blood centers is higher than that for one blood center serving the same demand.

Centralization of inventories also impacts wastage indicators, since the probability of using older units is usually higher than in a decentralized system. Another positive aspect of centralization is the increased efficiency of resources; decentralized systems usually have a large number of blood centers, but the annual production for many of them is typically low, since many supply products just for one or perhaps a few hospitals directly. Figure 5.2 presents an example of this situation in Colombia, where about 50% of the blood banks have an annual production lower than 5,000 units (INS 2016).

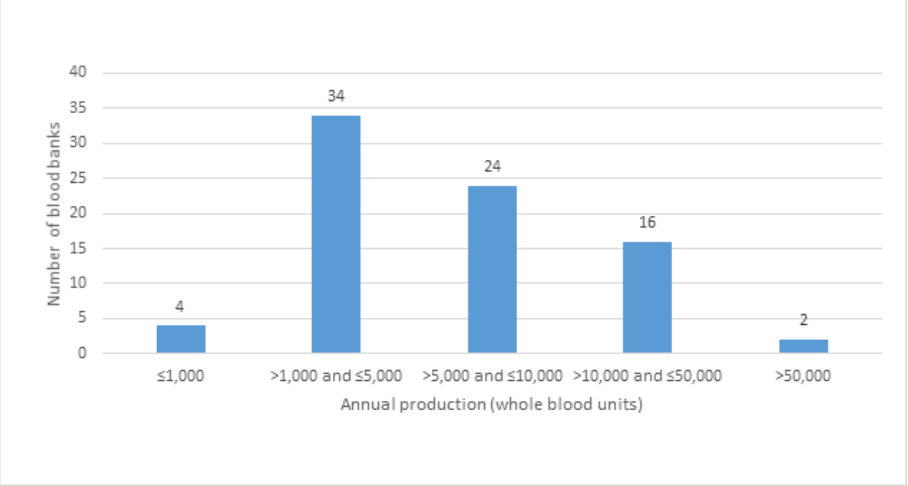


Figure 5.2: Number of blood banks in Colombia by annual production.

In addition, in a decentralized system competition can exist between blood banks in the same region, which can negatively affect the system as a whole. Decentralized systems often include different types of organization such as private blood centers, public blood centers and charitable institutions such as the Red Cross. The objectives of the players might differ, thus generating competition between organizations. Competition is most commonly associated with blood collection, since all institutions recruit donors from the same population, but is also observed in demand where competitive pricing and marketing strategies may be employed to increase the number of customers within a region.

Furthermore, decentralized systems may lead to suboptimal planning. Donation and demand patterns might differ among the regions because of local holidays; while one region could be at risk of shortage, another region could supply extra blood products. This impacts performance indicators, such as outdated units and stockouts, since blood inventories are usually allocated to only one or two hospitals in the same region.

5.2.2 Advantages of Decentralized systems

Despite the benefits of centralization, many examples of decentralized systems can be found. Most of these are in developing countries such as Brazil, where in 2012 there were 530 blood banks to collect about 3.3 million blood units. Venezuela has an even

more decentralized system: in 2012, there were 316 blood banks to collect about 445,000 blood units (PAHO 2015). However, some developed countries have decentralized systems as well. For example, the US has more than 79 blood centers, excluding internal blood centers found in hospitals, to serve a population of 330 million (AABB 2016). The reasons for keeping a decentralized structure may be different for every country; however, in general terms, large distances, high transportation costs and accessibility limitations can favor decentralized systems. Furthermore, decentralized networks can arise for political reasons, in order to maintain local control of operations.

Large distances and unreliable transportation systems may favor decentralization. Geography plays an important role when decentralization decisions are made. Long distances or unreliable transportation systems can increase the risk of stockouts in some regions. Sometimes, alternative transportation methods such as air transport can be used; however, depending on the volume of materials to be transported, a local blood center may be more economical in remote or distant regions.

Political aspects are also a common reason for decentralized systems. Such factors cannot be ignored, although this can be controversial since the benefits of centralization are well known for the whole system. However, blood centers also represent economic development and are generators of employment.

Finally, organizational diversity within a country's blood supply system can also favor decentralization. In regions with many different agencies such as the Red Cross, private and public centers and internal blood banks, a centralized strategy may be more difficult to implement.

5.2.3 From Decentralized to Centralized Systems

In general, the trend is towards centralization in developed countries, where only a very small number of different agencies control the national blood system. This is the case for the Canadian blood system, which has developed a centralization process which is still in progress.

Canada's blood supply chain is managed by two agencies: Canadian Blood Services and HémaQuébec. Canadian Blood Services (CBS) is the non-profit organization responsible for the management of the blood supply chain in all regions outside of the Province of Québec. CBS services a population of about 27 million people. Historically, each province in Canada had one or more blood centers within its boundaries. However, over the past decade, CBS has been engaged in a process of centralization in an effort to maximize productivity, enhance process standardization, and promote product availability. In 2005, CBS collected 850,000 units of whole blood, 50,000 units of plasma by apheresis, and 26,000 units of platelets by apheresis. To do so, it employed 4,400 persons and had 13 full service blood centers, each of which collected, tested, produced, and distributed blood products within a particular region (CBS 2006). In 2015, CBS collected approximately the same number of blood products, but did so employing 4,300 employees working in nine blood centers supported by two dedicated national testing laboratories (CBS 2016). Current plans suggest that by 2020, the CBS network will consist of two national testing laboratories, 6-8 blood centers (collection and production only), and 4 – 6 stock holding units.

In summary, centralization in the blood supply chain has multiple benefits. Apart from political decisions, centralization decisions are dominated by geographic conditions in the case of collection, production and distribution centers. Accordingly, the approach proposed here supports decisions such as the optimal number and capacity of blood facilities, including collection, production and distribution centers, whether for centralized or decentralized systems.

5.3 Materials and Methods

To find the optimal configuration of the blood supply chain and the optimal collection and production strategy, we employ mathematical programming. This technique allows us to formulate the problem with a defined structure. A mathematical programming model is composed of decision variables that represent the decisions to be made, and

constraints that make the model consistent in terms of use of resources and other conditions inherent to the system, such as distance limits. The solution to the model provides the optimal values for the decision variables, based on one or more objective functions. Typical objective functions in the blood supply chain can be, for example, minimization of total cost, minimization of the number of donors needed to meet demand, or minimization of stockouts and expired units.

A schematic representation of our model is presented in Figure 5.3 and the mathematical formulation is presented in Section 5.3.1.

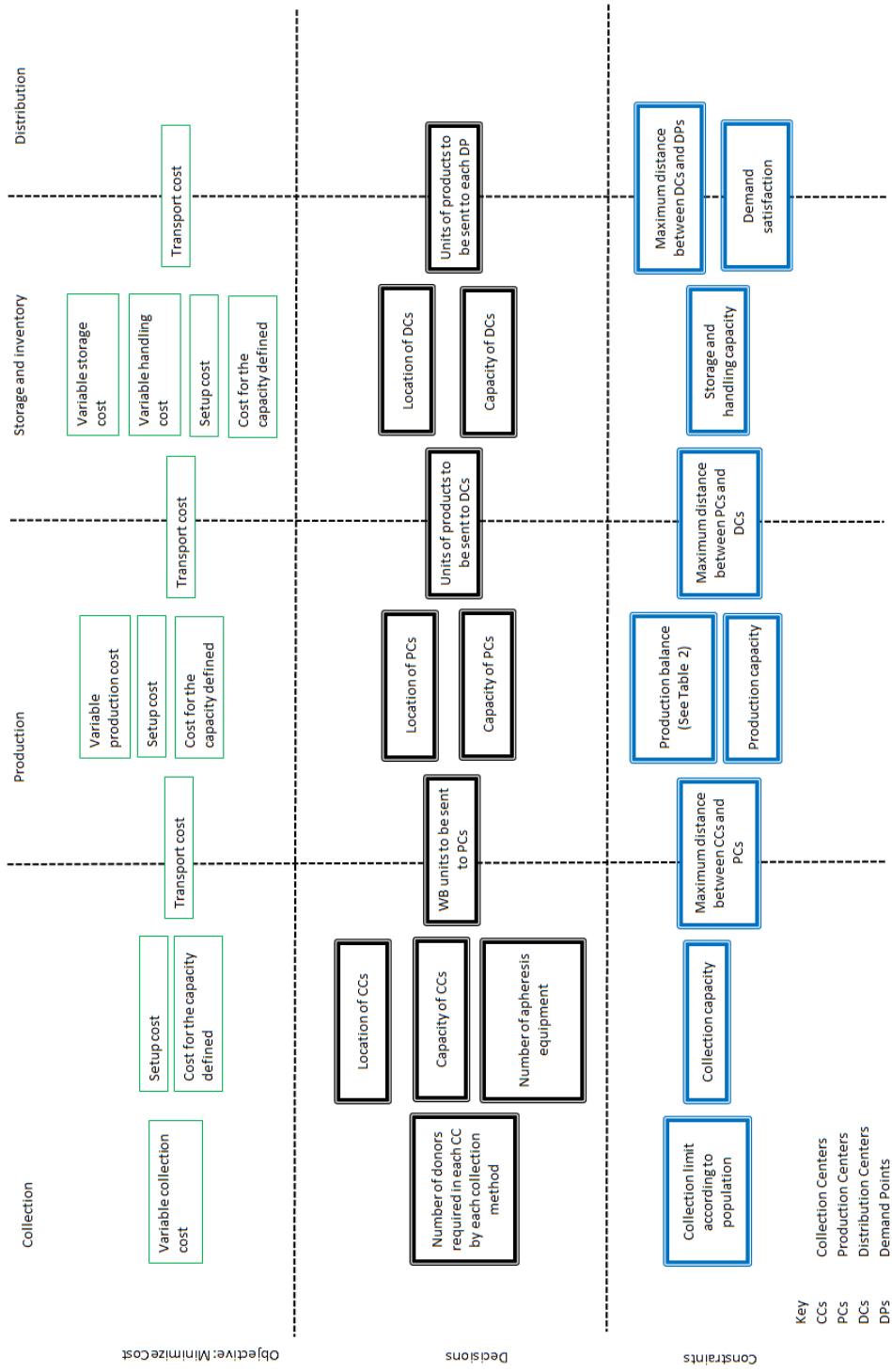


Figure 5.3: Schematic representation of the mathematical model for the design of the blood supply chain.

5.3.1 Mathematical Model

Definition of Sets

I	=	Set of location alternatives for collection centers - indexed by i.
J	=	Set of location alternatives for production centers - indexed by j.
K	=	Set of location alternatives for distribution centers - indexed by k.
L	=	Demand points - indexed by l.
W	=	Collection alternatives – indexed by w.
P	=	Products required – indexed by p.

Model Data (Information Provided)

β	=	Setup cost of a collection center [$]
β^{cap}	=	Fixed cost for each package of capacity [$/10,000 units]
ϕ	=	= Setup cost of a production center [$]
ϕ^{cap}	=	Fixed cost for each package of capacity [$/10,000 units]
γ	=	Setup cost of a distribution center [$]
γ^{cap}	=	Fixed cost for each package of capacity [$/10,000 units]
χ	=	Fixed cost of one piece of RBC apheresis collection equipment [$]
δ	=	Fixed cost of one piece of platelets apheresis collection equipment [$]
η_w	=	Collection cost of assigning one donor to the process w, $w \in W$. [$/donor]
φ_{ij}	=	Transport cost of a unit of product between the collection center i to the production center j, $i \in I$, $j \in J$.[$/unit]
κ_{jk}	=	Transport cost of a unit of product between the production center j to the distribution center k, $j \in J$, $k \in K$.[$/unit]
λ_{kl}	=	Transport cost of a unit of product between the distribution center k to the demand point l, $k \in K$, $l \in L$.[$/unit]
μ_p	=	Storage cost of a unit of product p, $p \in P$.[$/unit]
π_p	=	Handling cost of a unit of product p, $p \in P$.[$/unit]
θ_p	=	Variable processing cost of product p, $p \in P$.[$/unit]

α	=	Penalty for stockout. [$/unit]
E_i	=	Population of collection zone i, $i \in I$.
A_{jk}	=	Average time between shipments from production center j and distribution center k, $j \in J$, $k \in K$.[days]
C_{pw}	=	Units of product p obtained by assigning one donor to collection process w, $p \in W$, $p \in W$.
D_{lp}	=	Demand for product p in demand point l, $p \in P$, $l \in L$, [Units of product].
σ_p	=	Demand variability of product p, $p \in P$. [%]
F	=	Additional capacity for each package added in collection centers.[units]
H	=	Capacity of one piece of equipment of red blood cell apheresis collection. [donors]
U	=	Capacity of one piece of equipment of platelets apheresis collection. [donors]
N	=	Additional capacity for each added package in distribution centers. [units]
O	=	Additional capacity for each added package in production centers.
X	=	Maximum percentage of population assumed to donate blood.
Z	=	Inventory cycle stock.
R_p^{prod}	=	Historical discard rate of the product in production p, $p \in P$. [%]
R_p^{stor}	=	Historical discard rate of the product in storage p, $p \in P$. [%]
S_{pk}	=	Security stock factor for product p in the distribution center k, $p \in P$, $k \in K$.
$d^{CCs-PCs}$	=	Maximum travel time allowed between collection points and production centers. [hours]
$d^{PCs-DCs}$	=	Maximum travel time allowed between production centers and distribution centers. [hours]

$d^{DCs-DPs}$ = Maximum travel time allowed between distribution centers and demand points. [hours]

T_{ij} = Binary parameter, 1 if travel time between i and j is less than or equal to $d^{CCs-PCs}$, $i \in I$, $j \in J$.

V_{jk} = Binary parameter, 1 if travel time between j and k is less than or equal to $d^{PCs-DCs}$, $j \in J$, $k \in K$.

Y_{kl} = Binary parameter, 1 if travel time between k and l is less than or equal to $d^{DCs-DPs}$, $k \in K$, $l \in L$.

Decision Variables

r_i = Number of red blood cells apheresis equipment in zone i, $i \in I$.

p_i = Number of platelets apheresis equipment in collection zone i, $i \in I$.

f_i = 1 if a collection center is opened in site i, 0 otherwise, $i \in I$.

f_i^{cap} = Number of capacity packages assigned to the collection center located in i, $i \in I$.

v_j = 1 if a production center is opened in site j, 0 otherwise, $j \in J$.

v_j^{cap} = Number of capacity packages assigned to the production center located in j, $j \in J$.

w_k = 1 if a distribution center is opened in the site k, 0 otherwise, $k \in K$.

w_k^{cap} = Number of capacity packages assigned to the distribution center located in k, $k \in K$.

x_{ijw} = Number of donors to be processed by the method w in collection zone i and whose products will be processed in production center j, $i \in I$, $j \in J$, $w \in W$.

z_{jkp} = Units of product p to be sent from production center j to distribution center k, $j \in J$, $k \in K$, $p \in P$.

s_{klp} = units of product p to be sent from distribution center k to demand zone l, $k \in K$, $l \in L$, $p \in P$.

Auxiliary Variables

m_{lp} = Estimated stockout of product p in demand point l, $p \in P$, $l \in L$ [Units].

Decision variables considered in our model (shown in Figure 5.3) are aimed at supporting decisions in the four echelons of the blood supply chain. In the collection stage we include decisions on the location and capacity of collection centers; this also includes the number of apheresis machines needed to meet RBC and platelet apheresis requirements. The total number of donors required for each collection method is obtained. In production, the decision variables define the location and capacity of blood production centers, as well as the number of units to be processed in each center. Finally, in the inventory and storage stage, we consider the location and capacity of distribution centers. At this strategic level, the allocation of demand zones to distribution centers is determined, including the strategy to supply demand.

Objective Function

$$\begin{aligned}\min W = {} & \sum_{i\in I}(\beta f_i + \chi r_i + \delta p_i + \beta^{cap} f_i^{cap}) + \sum_{j\in J}(\phi v_j + \phi^{cap} v_j^{cap}) + \\ & \sum_{k\in K}(\gamma w_k + \gamma^{cap} w_k^{cap}) + \\ & \sum_{w\in W}\sum_{j\in J}\sum_{i\in I}\eta_i x_{ijw} + \sum_{p\in P}\sum_{l\in L}\sum_{k\in K}\pi_p s_{klp} + \\ & \sum_{j\in J}\sum_{k\in K}\sum_{p\in P}((Z\mu_p A_{jk} + \mu_p S_{pk}\sigma_p) + \theta_p) z_{jkp} + \\ & \sum_{w\in W}\sum_{j\in J}\sum_{i\in I}\varphi_{ij} x_{ijw} + \sum_{j\in J}\sum_{k\in K}\sum_{p\in P}\kappa_{jk} z_{jkp} + \\ & \sum_{k\in K}\sum_{l\in L}\sum_{p\in P}\lambda_{kl} s_{klp} + \sum_{p\in P}\sum_{l\in L}\alpha m_{lp} +\end{aligned} \tag{5.1}$$

Equation (5.1) represents the objective function to be optimized which minimizes the total cost. The first term computes the fixed cost for collection centers and equipment for apheresis for RBCs and platelets. The second term computes the fixed costs for production centers according to the capacity defined. The third term calculates the

fixed cost for operating the distribution centers according to capacity, while the fourth term calculates the collection cost. The fifth term calculates the handling cost for all units in the distribution centers. The sixth term computes the production cost and the inventory cost composed of cycle and safety stock. Terms seven, eight and nine compute the transport cost between collection and production centers, productions and distribution centers and distribution centers and demand points respectively. Finally, the last term penalizes stockouts.

In our model, the objective is the minimization of a cost function over one-year period. The costs considered in our model are presented in Figure 3. This cost function comprises the fixed costs for the facilities, variable collection and production costs, variable handling costs, and inventory and transport costs as well as penalties for stockouts. Fixed costs for the facilities include a setup cost associated with the physical facility and a step-cost based on the capacity chosen (fixed costs are estimated for a one-year period). For example, fixed costs for production centers include physical building, equipment, labor, maintenance and training. Different items are considered in the step-cost, depending on the function of each facility; these costs are pre-defined as options for each potential site. Variable costs include the cost of collecting from a donor, for each collection method included in the model, and the cost of production for the number of units processed. At distribution centers, variable costs consider both the cost of keeping inventory and the handling cost for units dispatched. Finally, transport costs are the costs of transporting the required units of blood between different stages, according to a fixed, predefined transportation plan.

To apply the model to any specific case, appropriate costs must be included. Since this paper is aimed at presenting a generally applicable approach with a discussion about the design of blood supply chains, the costs used in the example below were all obtained from information in the public domain. The fixed cost data were obtained from PAHO (2005) and adjusted where necessary. Transport costs were assumed to be a function of travel time, and were obtained using Google Maps. Variable costs were extracted from PAHO (2005); inventory cost and handling cost were assumed to be a percentage of the value of the product.

Constraints

Decisions about the supply of the blood supply chain must meet multiple constraints: the model proposed in this paper considers the following:

- Demand is defined by region, and is stochastic (i.e., uncertain);
- There is a defined maximum percentage of the population donating blood in regions where a collection center is located;
- Collection, production and distribution are subject to the capacity defined by the model;
- The number of products obtained comes from the application of collection methods in Table 5.1 and the number of donors assigned to each collection process. This number, however, is adjusted by a historical discard rate;
- The maximum distances between the different stages are predefined by the decision-maker.
- Stockouts are not desirable and are penalized in the model;
- Inventory is modeled only in distribution centers;
- Apheresis collection processes can be carried out in whole blood collection centers.

$$\sum_{j\in J}\sum_{w\in W} x_{ijw} \quad \leq \quad XE_i, \quad \forall i \in I \tag{5.2}$$

$$\sum_{j\in J}\sum_{w=1,2,3\in W} x_{ijw} \quad \leq \quad Ff_i^{cap}, \quad \forall i \in I \tag{5.3}$$

$$\sum_{j\in J} x_{ij4} \quad \leq \quad Hr_i, \quad \forall i \in I \tag{5.4}$$

$$\sum_{j\in J} x_{ij5} \quad \leq \quad Up_i, \quad \forall i \in I \tag{5.5}$$

$$\sum_{i\in I}\sum_{w\in W} C_{wp}x_{ijw}(1-R_p^{prod}) \quad = \quad \sum_{k\in K} z_{jkp}, \quad \forall j \in J, p \in P \tag{5.6}$$

$$\sum_{k \in K} z_{jk2} \quad \leq \quad Ov_j^{cap}, \quad \forall j \in J \tag{5.7}$$

$$\sum_{k \in K} \sum_{p \in P} s_{klp} \quad \leq \quad Nw_k^{cap}, \quad \forall k \in K \tag{5.8}$$

$$x_{ijw} \quad \leq \quad T_{ij}M, \quad \forall i \in I, j \in J, w \in W \tag{5.9}$$

$$z_{jkp} \quad \leq \quad V_{jk}M, \quad \forall j \in J, k \in K, p \in P \tag{5.10}$$

$$s_{klp} \quad \leq \quad Y_{kl}M, \quad \forall k \in K, l \in L, p \in P \tag{5.11}$$

$$\sum_{k \in K} s_{klp} + m_{lp} \quad \geq \quad D_{lp}, \quad \forall l \in L, p \in P \tag{5.12}$$

$$\sum_{j \in J} z_{jkp}(1 - R_p^{stor}) \quad \geq \quad \sum_{l \in L} s_{klp}, \quad \forall k \in K, p \in P \tag{5.13}$$

$$f_i^{cap} \quad \leq \quad f_i M, \quad \forall i \in I \tag{5.14}$$

$$v_j^{cap} \quad \leq \quad v_j M, \quad \forall j \in J \tag{5.15}$$

$$w_k^{cap} \quad \leq \quad w_k M, \quad \forall w \in W \tag{5.16}$$

$$r_i \quad \leq \quad f_i M, \quad \forall i \in I \tag{5.17}$$

$$p_i \quad \leq \quad f_i M, \quad \forall i \in I \tag{5.18}$$

$$x_{ijw}, z_{jkp}, s_{klp}, m_{lp} \in \mathbb{R}^+ \tag{5.19}$$

$$f_i, v_j, w_k \in \{0, 1\} \tag{5.20}$$

$$r_i, p_i, f_i^{cap}, v_j^{cap}, w_k^{cap} \in \mathbb{Z}^+ \tag{5.21}$$

Constraints (5.2) limit the collection according to the population. Constraints (5.3) - (5.5) guarantee that the collection of whole blood, RBCs by aphaeresis and platelets by aphaeresis does not exceed the capacity available respectively. Constraints (5.6) compute the total number of units produced and make this equal to the units dispatched to the distribution centers. Constraints (5.7) guarantee that the units processed in the production centers (RBC by fractionation) do not exceed capacity, while Constraints (5.8) guarantees than the number of units dispatched from the distribution center do

not exceed capacity. Constraints (5.9) – (5.11) limit the distances for allocation of collection to production centers, production centers to distribution centers and demand points to distribution centers respectively. Constraints (5.12) guarantee that the units dispatched plus the stockouts will be equal to the demand. Constraints (5.13) guarantee the consistency and flow balance in the distribution centers. Constraints (5.14) – (5.16) guarantee that capacity units are only assigned to opened facilities. Constraints (5.17) and (5.18) limits the use of aphaeresis collection equipment only to a collection centers opened. Finally Constraints (5.19) – (5.21) define the domain of the decision variables.

5.3.2 Consideration of Uncertainty in Demand

The model proposed in Equations (5.1) - (5.21) corresponds to a deterministic version of the problem. In order to present the model as a two-stage stochastic optimization problem and introduce the solution methodology, the formulation is expressed as follows:

$$\min_{y} f(y) = c^T y + E[Q(y, \xi)] \tag{5.22}$$

subject to:

$$y_{bin} \in \{0,1\}^{|I|+|J|+|K|},\ y_{int} \in \mathbb{Z}^{3|I|+|J|+|K|},\ y_{bin},\ y_{int} \in y \tag{5.23}$$

In this notation, c represents a cost vector related to first stage decisions. In the specific case of the model presented in this article, those decisions are related to the location and capacity of the facilities. The term y is then a vector composed of binary variables represented by y_{bin} associated with the location of facilities and integer variables represented by y_{int} associated with the capacity of facilities. Both, y_{bin} and y_{int} represent the first stage decision variables in our model. The values of $|I| + |J| + |K|$ and $3|I| + |J| + |K|$, relate to the problem size, in other words, how many binary and integer first level variables are optimized. The term $Q(y, \xi)$ refers to the optimal value of the following optimization problem:

$$
\begin{aligned}
Q(y,\xi) = \min \quad & \sum_{i\in I}(\beta f_i + \chi r_i + \delta p_i + \beta^{cap} f_i^{cap}) + \sum_{j\in J}(\phi v_j + \phi^{cap} v_j^{cap}) + \\
& \sum_{k\in K}(\gamma w_k + \gamma^{cap} w_k^{cap}) + \\
& \sum_{w\in W}\sum_{j\in J}\sum_{i\in I}\eta_i x_{ijw} + \sum_{p\in P}\sum_{l\in L}\sum_{k\in K}\pi_p s_{klp} + \\
& \sum_{j\in J}\sum_{k\in K}\sum_{p\in P}((Z\mu_p A_{jk} + \mu_p S_{pk}\sigma_p) + \theta_p) z_{jkp} + \\
& \sum_{w\in W}\sum_{j\in J}\sum_{i\in I}\varphi_{ij} x_{ijw} + \sum_{j\in J}\sum_{k\in K}\sum_{p\in P}\kappa_{jk} z_{jkp} + \\
& \sum_{k\in K}\sum_{l\in L}\sum_{p\in P}\lambda_{kl} s_{klp} + \sum_{p\in P}\sum_{l\in L}\alpha m_{lp} +
\end{aligned}
\tag{5.24}
$$

subject to constraints (5.2) – (5.11), (5.13) – (5.21) and to:

$$
\sum_{k\in K} s_{klp} + m_{lp} \quad \geq \quad D_{lp}(\xi), \quad \forall l \in L, p \in P \tag{5.25}
$$

In constraint (25), ξ represents a random vector associated with the stochastic nature of the demand. The optimal value for the problem (5.2) – (5.11), (5.13) – (5.21) , (5.22) and (5.23) is a function of the first level variables y, and a particular realization of the random vector ξ. The probability distribution function for the random vector is assumed to be known so that the expected value can be obtained. Using a sampling average approach, the expected value $E[Q(y,\xi)]$ can be calculated taking the average of the individual values of the samples of size N. In the particular context of this work the resulting model is mixed integer and linear. The problem can be re-stated as follows:

$$
\min_{y}\{\hat{f}_N(y) = c^T y + \frac{1}{N}\sum_{n=1}^{N} Q(y,\xi^n)\} \tag{5.26}
$$

The SAA method proposes a methodology to deal with the uncertainty using sampling. The logic of the algorithm is simple, generating samples of the random vector ξ and solving one deterministic model for each realization of the samples generated. However, the model needs to solve simultaneously N scenarios, which increase considerably the number of second stage variables and constraints. The algorithm also allows evaluation of

the convergence for different sample sizes, in terms of an estimated optimality gap and its variance. The SAA problem can be difficult to solve; in order to find a good configuration for the blood supply chain we propose a heuristic based on the SAA algorithm. The complete methodology to solve the problem presented in equation 5.26 is described below.

5.3.3 Solution Methodology - Heuristic Based on the Sample Average Approximation Algorithm

The model described in Sections 5.3.1 to 5.3.3 can be solved mathematically for an estimated demand based on forecasts or expert judgement. However, the solution obtained can have limitations especially when the variability of demand is high. One of the most important aspects when designing the blood supply chain is consideration of uncertainty in the parameters. We consider uncertainty in demand, but the approach is applicable for uncertainty in any of the parameters. The approach is based on a technique called Sample Average Approximation (SAA) which is focused on the consideration and analysis of multiple scenarios simultaneously (Santoso et al. 2005). These scenarios are generated by sampling of probability distributions fitted from historical data. Then, the process is repeated several times to evaluate the convergence of the solutions obtained.

This approach has been widely used for industrial supply chains which face similar location-allocation problems. However, solving multiple scenarios at the same time makes the model difficult to solve, requiring hours, days or even years to obtain a solution, depending on the size of the system analyzed. This obviously can be impractical in many cases. For this reason, we propose a heuristic or approximated method based on the SAA approach that allows near optimal solutions to be obtained in a reasonable computation time. In general terms the heuristic solves the model for individual scenarios and looks at “good” and “bad” locations based on the number of appearances in the individual scenarios. These decisions are then fixed and the model is solved again considering all scenarios simultaneously, but also integrating information about the good and bad locations found during the first step. The solution algorithm is described as follows:

Step 1: Generate M independent samples, each of size N:(ξ_j^1,...,ξ_j^N), for j = 1, ..., M.For each scenario of each sample solve the deterministic model (given that at this point we are just trying to find good locations the models do not need to be solved to optimality). For each sample j, fix the first level variables based on the individual results of the each of the N scenarios and the rules defined as follows:

The idea is to find locations that are highly probably to appear in the optimal solution of the stochastic problem and fix them in order to make the SAA problem easier to solve. The criteria to do this can vary depending on the problem. In our case we fixed locations that appear in at least 70% of the scenarios. In addition we discard locations that only appear in at most 30% of the number of scenarios. This is done for location decisions.

In the case of capacity decisions, for each sample we choose the minimum capacity of each facility found during the solution of the individual scenarios. Then we add a constraint in the SAA problem doing the decision variable greater or equal to the minimum capacity found. In other words, the minimum capacity found during the individual executions is set as a minimum bound in the SAA problem.

Step 2: Considering the fixed first level variables found in Step 1, solve the corresponding SAA problem (Equation 5.26) for every sample j. Let v_N^j and $\hat{y}_N^j$, for j = 1, ..., M, represent the optimal value and optimal solution respectively.

Step 3: Calculate the following statistical indicators:

$$\bar{v}_{N,M} = \frac{1}{M}\sum_{j=1}^{M} v_N^j \tag{5.27}$$

,

$$\sigma^2_{\bar{v}_{N,M}} = \frac{1}{M(M-1)}\sum_{j=1}^{M}(v_N^j - \bar{v}_{N,M})^2 \tag{5.28}$$

,

Step 4: Select a solution $\bar{y} \in Y$ for the original problem, using one of the $\hat{y}_N^j$ solutions already obtained. Estimate the true objective value $f(\bar{y})$ by using the expression:

$$\tilde{f}_{N'}(\bar{y}) = c^T\bar{y} + \frac{1}{N'}\sum_{n=1}^{N'} Q(\bar{y}, \xi^n) \tag{5.29}$$

,

where $(\xi^1,\ldots,\xi^{N'})$ is an independent sample of size N'. It is expected that N' is considerably larger than the sample size N used in step 1. Obtain the variance as follows:

$$\sigma^2_{N'}(\bar{y}) = \frac{1}{N'(N'-1)}\sum_{n=1}^{N'}(c^T\bar{y} + Q(\bar{y}, \xi^N) - \tilde{f}_{N'}(\bar{y}))^2 \tag{5.30}$$

,

Step 5: Calculate the optimality estimator based on the results from steps 3 and 4.

$$gap_{N,M,N'} = \tilde{f}_{N'}(\bar{y}) - \bar{v}_{N,M} \tag{5.31}$$

$$\sigma^2_{gap} = \sigma^2_{N'}(\bar{y}) + \sigma^2_{\bar{v}_{N,M}} \tag{5.32}$$

,

5.4 Data and Case Study

The blood supply chain in Colombia consists of 82 blood banks and 414 transfusion services, which are distributed among 32 regions and the capital, Bogota. The largest number of blood centers in the same region is found in Bogota, where 15 blood banks supply blood products for 68 transfusion points. In addition, seven regions have transfusion points but no blood banks. These regions must be supplied from other geographical areas. In recent years, the number of blood banks in Colombia has decreased: in 2002, there were 161 (PAHO 2002). However, the system remains highly decentralized, which means that indicators such as the outdating rate and cost can be higher than for centralized systems. In Colombia, the national blood bank network is controlled by the National Institute of Health, which defines legal aspects of the network, as well as the national blood policy. The network comprises different agencies, including large public and private blood centers and small internal blood centers for large hospitals. Arguably

this level of decentralization and diversity of agencies can cause competition in donor recruitment and lead to inefficiencies in the system and unnecessary high costs.

Another feature of the Colombian system is the difference in collection strategies throughout the country; each region defines its own collection goals for blood and blood products using local decision rules. The highest proportion of platelets collected by apheresis in 2012 was in the Valle del Cauca region at 93%, followed by Antioquia at 42%. However, most regions obtain platelets from whole blood donations. On the other hand, the highest proportion of RBCs produced by apheresis occurred in the Tolima region, at 8.24%, followed by 6.26% from Bogota. Again, most regions obtain RBCs exclusively from whole-blood donations.

Thus in our model we consider 32 feasible locations for collection and production centers which correspond to the regional capital cities, and 36 feasible locations for distribution centers; this selection was made by considering the current location of blood banks. We grouped the 414 transfusion centers by city and considered 120 demand points (cities). The aggregate demand for one year includes 610,883 RBCs, 252,840 platelets, as well as 204,908 units of plasma and 33,682 of cryoprecipitate. The main data source for the case study is available online and published by the Instituto Nacional de Salud (INS 2013). The probability distributions for yearly demand are assumed to be triangular, since there is not enough information available to apply statistical procedures to fit a probability distribution.

In the example used, we assume that, at most, 4% of the population will donate blood; this percentage is calculated based on historical donations from this population. In practice, this percentage may differ between regions; however, in the case study we assume it is uniform throughout the country.

5.5 Scenarios

As mentioned in Section 5.1, our approach is flexible and allows several aspects, such as uncertainty, preferences and alternatives, to be modeled with relatively few modifications to the original mathematical framework. Firstly, we can analyze several configuration

policies for the network by varying the lead times allowed between the different stages. Secondly, the model also allows us to study the collection strategy; specifically, the impact of combining apheresis and whole blood collection.

5.5.1 Configuration Policies

In this first set of scenarios we study the impact on the configuration of the network of assuming different travel times between stages. Seven different scenarios are studied (see Table 5.2) to obtain the configurations of the network under different conditions. Given the relevance of the travel time between donation and production centers, and the travel time from distribution centers to demand points, the model is required to meet strict maximum travel time constraints at this stage in all scenarios. The distance between production and distribution centers is constrained in Scenarios S1 and S2, but in Scenarios S3 - S7 this distance is not limited (this feature is represented by the letter M) which allows the model to define the location and capacity of production centers based exclusively on cost. Scenarios S1 to S7 present different levels of centralization, where S1 and S7 represent the most extreme decentralized and centralized scenarios respectively.

Table 5.2: Scenarios studied based on maximum travel time

Maximum travel time	Scenarios						
	Decentralized.....Centralized						
	S1	S2	S3	S4	S5	S6	S7
From CCs to PCs (hours)	3	4	3	4	3	4	5
From PCs to DCs (hours)	3	4	M	M	M	M	M
From DCs to DPs (hours)	3	4	3	4	5	5	5

CCs = Collection centers, PCs = Production centers,
DCs = Distribution centers, DPs = Demand points,
M = No distance constraint.

These scenarios consider variations of maximum travel times; however, the model can also consider several other aspects, independently or simultaneously, such as:

- The design of the network given a specific budget.
- The location and design of the network given a fixed number of facilities

- The design of the network given local policies of coverage
- The design of the network for decentralization constraints
- The collection, production and distribution strategy given an already-defined network
- The impact of increasing the percentage of donations for each or all of the collection centers

5.5.2 Whole Blood vs Apheresis

The model can be used to study the impact of using apheresis processes with varying extents on the configuration of the network (location and capacity of the facilities) and on the number of donors and the cost of operations. In these scenarios, we constrain the model to produce a certain percentage of RBCs and platelets using apheresis. The model seeks the best configuration under these policies, demonstrating the impact of apheresis on the number of facilities and other performance indicators, such as cost and number of donors. To evaluate the impact of the use of apheresis, we present four scenarios that represent different percentages of the minimum number of units produced by apheresis. In Scenario A1, apheresis is not used; in Scenario A2, 25% of RBCs are obtained using apheresis; Scenario A3 produces 25% of units of platelets from apheresis, and finally in Scenario A4 the model produces 25% of RBCs and 25% of platelets using apheresis processes.

Additional constraints when a minimum percentage of products obtained from apheresis is required.

p^{RBC} = minimum percentage of RBCs required obtained by using apheresis. p^{PLT} = minimum percentage of Platelets required obtained by using apheresis.

$$\sum_{j\in J}\sum_{i\in I} 2x_{ij4} \quad \geq \quad p^{RBC}\Big(\sum_{w=1,2,3\in W}\sum_{j\in J}\sum_{i\in I} x_{ijw} + 2\sum_{j\in J}\sum_{i\in I} x_{ij4}\Big) \tag{5.33}$$

$$10\sum_{j\in J}\sum_{i\in I} x_{ij5} \quad \geq \quad p^{PLT}(\sum_{w=1,2,3\in W}\sum_{j\in J}\sum_{i\in I} x_{ijw} + 10\sum_{j\in J}\sum_{i\in I} x_{ij5}) \tag{5.34}$$

5.6 Results

5.6.1 Policies

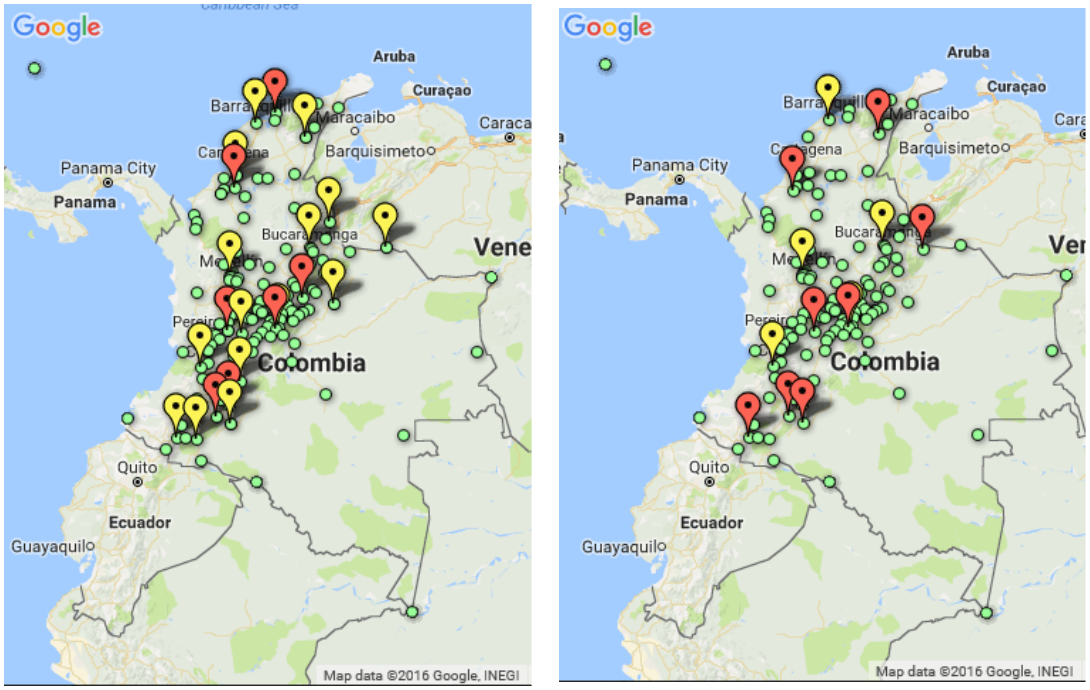
Table 5.3 presents detailed results of the application of the model to the demand data for the case study, assuming the travel time constraints listed in Table 5.2. We chose Scenarios S1 and S7 to explain the results, since these represent the extremes of decentralized and centralized scenarios respectively. Scenario S7, with the longest travel times permitted, presents the most centralized configuration: in this case only 5 production centers are opened, in contrast to 15 for decentralized Scenario S1. Collection is also centralized in 10 collection centers in contrast to 17 for S1. In addition, S7 uses only 13 distribution centers, compared to 22 in S1. The number of donors is lowest in Scenario S1; however, this scenario presents the highest number of stockouts. This means that several regions are not able to meet the distance constraints of scenario S1; this scenario is likely impractical given the high number of stockouts. The cost of Scenario S1 is considerably higher than that of Scenario S7, since stockouts are highly penalized in the objective function of the model. However, this result remains valid even if the cost of stockouts is not considered. It should be noted that the total capacity required is also greater for Scenario S1 than for S7; however, since the number of donors is lower, the use of the capacity is lower in this scenario.

Table 5.3: Summary of solutions obtained under different scenarios on maximum travel time.

Decision		S1	S2	S3	S4	S5	S6	S7
Collection Centers	Number	17	15	9	10	11	11	10
	Number of capacity packages required WB	68	67	66	66	67	67	67
	Apheresis RBCs equipment	3	4	2	2	2	2	2
	Apheresis platelets equipment	1	0	0	0	0	0	0
Production centers	Number	15	10	5	4	5	5	5
	Number of capacity packages required	69	67	66	66	67	67	67
Distribution Centers	Number	22	18	23	17	13	13	13
	Number of capacity packages required	114	111	114	111	112	112	112
Average number of donors required	Triplex bag (thousand)	236	241	245	248	252	253	252
	Quadruple bag – Alt. A (thousand)	349	361	358	361	365	365	365
	Quadruple bag – Alt. B (thousand)	43	45	45	45	45	45	45
	RBCs by apheresis (thousand)	3	5	1	1	2	2	2
	Platelets by apheresis (thousand)	0	0	0	0	0	0	0
Average total donors (thousand)		632	651	649	655	664	665	665
Average stockouts (thousand)		49	16	24	16	0	0	0
Average cost ($ million)		$85.20	$51.80	$58.20	$50.40	$34.80	$34.70	$34.60

WB = Whole Blood

Figure 5.4 presents a geographical comparison between results of the two scenarios analyzed. Yellow (lighter) icons represent locations where both a production center and a distribution center are recommended. Red (darker) icons represent only distribution centers and small green circles represent demand points.



(a) Scenario S1 (b) Scenario S7

Figure 5.4: Geographical representation of the facility locations under the (a) Scenario S1, (b) and Scenario S7.

Finally, one of the important outputs from our model is the optimal collection and fractionation strategy for each collection center. Table 5.4 presents the optimal collection rate for each collection center for Scenario S7. The aggregated or national collection strategy indicates that 37.9% percent of the blood should be collected using a triplex bag, while 61.8% should be collected using a quadruple bag, with the remaining 0.3% of donors assigned to RBCs by apheresis. However, according to Table 5.4, the collection strategy varies for the different collection centers. For example, the percentages for the blood collection center located in Medellín are 40% and 60% for triplex bag and quadruple bag respectively. Conversely, the values for the collection center located in Pereira are 64% and 36% respectively for the same collection alternatives. This is due to the difference in collection and transportation costs. Production centers will always try firstly to use blood collected in the same city (to avoid transportation costs), but if the amount

of blood collected is insufficient to meet demand it must be supplemented with blood collected from a nearby city. For example, blood collection centers in Bucaramanga and Cúcuta both collect blood for the production center located in Bucaramanga. However, given collection costs, the model will try to use triplex bag first (the cheapest collection method). For this reason the collection rate for triplex bag is higher in Cúcuta than Bucaramanga . However, the cost is not the only factor that affects the rates; the model can make use of other collection methods if the demand for other products has not been supplied with the blood collected in the same location as the production center.

Table 5.4: Optimal collection strategy for each collection center in the Scenario S7 "Centralized".

Collection Center	Maximum donor population	Number of donors required	Collection Process	Number of bags to be processed by production center						
				Medellín	Barranquilla	Bogotá, D.C.	Bucaramanga	Cali	Total	% per process
Medellín	98,573	98,573	Triple Bag	39,430	0	0	0	0	39,430	40%
			Quadruple Bag	59,143	0	0	0	0	59,143	60%
Barranquilla	48,739	48,739	Triple Bag	0	18,794	0	0	0	18,794	39%
			Quadruple Bag	0	29,945	0	0	0	29,945	61%
Bogotá, D.C.	315,151	309,738	Triple Bag	0	0	99,639	0	0	99,639	32%
			Quadruple Bag	0	0	210,099	0	0	210,099	68%
Cartagena	40,070	40,029	Triple Bag	0	21,157	0	0	0	21,157	53%
			Quadruple Bag	0	18,500	0	0	0	18,500	46%
			RBCs by apheresis	0	371	0	0	0	371	1%
Popayán	11,101	10,000	Triple Bag	0	0	0	0	4,747	4,747	47%
			Quadruple Bag	0	0	0	0	5,253	5,253	53%
Cúcuta	26,000	17,631	Triple Bag	0	0	0	14,449	0	14,449	82%
			Quadruple Bag	0	0	0	3,182	0	3,182	18%
Armenia	11,867	10,000	Triple Bag	0	0	0	0	4,192	4,192	42%
			Quadruple Bag	0	0	0	0	5,808	5,808	58%
Pereira	18,784	18,395	Triple Bag	322	0	0	0	11,503	11,826	64%
			Quadruple Bag	204	0	0	0	6,365	6,569	36%
Bucaramanga	21,116	20,000	Triple Bag	0	0	0	4,320	0	4,320	22%
			Quadruple Bag	0	0	0	15,680	0	15,680	78%
Cali	94,792	91,433	Triple Bag	0	0	0	0	33,565	33,565	37%
			Quadruple Bag	0	0	0	0	56,435	56,435	62%
			RBCs by apheresis	0	0	0	0	1,433	1,433	2%
National	686,192	664,538	Triple Bag						252,118	37.90%
			Quadruple Bag						410,615	61.80%
			RBCs by apheresis						1,804	0.30%
Total				99,099	887,68	309,738	37,631	129,302	664,538	

As seen in Table 5.4, the solution obtained for Scenario S7 recommends the acquisition of two RBC apheresis machines for the Cartagena and Cali collection centers. In the case of Cartagena, this occurs because of the constraints with the maximum percentage of donors in the regions. In contrast, in Cali the available number of donors could cover the constraint, but it would be necessary to expand the capacity by 10,000 units, which is more expensive than obtaining that number of RBCs using apheresis. However, the number of donors allocated to this process is low in both locations and thus the decision-maker may wish to consider whether the collection center could simply increase the whole blood collection and the capacity in this region so that all the demand is satisfied from fractionation. We have used a step capacity of 10,000 units; however, this figure can be defined according to the system since for small countries this value can be impractical.

In addition, our model also allows the optimal fractionation strategy to be found. From Table 5.5 it can be seen that the optimal fractionation strategy nationwide is 89% for quadruple bags alternative A (RBCs, plasma, and platelets) and 11% for alternative B (RBCs and cryoprecipitate). These values are similar for all production centers. Results from Tables 5.4 and 5.5 show that that decisions regarding collection and fractionation strategies are important for the determination of performance indicators for the blood supply chain such as cost and number of donors.

Table 5.5: Optimal fractionation strategy for quadruple bags

Production Center	**Fractionation strategy**				
	Total quadruple bags	**Alternative A**	**%**	**Alternative B**	**%**
Medellín	59,347	52,829	89%	6,518	11%
Barranquilla	48,446	44,418	92%	4,027	8%
Bogotá, D.C.	210,099	184,429	88%	25,670	12%
Bucaramanga	18,862	17,170	91%	1,692	9%
Cali	73,862	66,585	90%	7,277	10%
National	410,615	365,432	89%	45,183	11%

5.6.2 Whole Blood vs Apheresis

The use of apheresis products has an impact on system cost and the number of donors required to meet demand. Table 5.6 presents the network configurations for the four

scenarios (A1 - A4) that represent different combinations of whole blood and apheresis, based on scenario S7. Table 5.6 also presents costs, numbers of donors and stockouts. As expected, the lowest cost is obtained when all the products are obtained from whole blood. The use of apheresis in the case of platelets does not have a considerable impact on the cost or number of donors; while the collection cost is higher it is compensated for by the efficiency of the collection process, since up to 10 standard units (1-2 adult doses) can be obtained using this method. Furthermore, the impact of collecting platelets by apheresis on the number of donors is low, since the number of donors is largely dictated by the number of RBCs required. This is different in the case of RBCs obtained from apheresis. The cost is increased when this type of collection is used; since only two units can be obtained using this process. However, as the percentage of RBCs obtained from apheresis is increased, the number of donors required to fill demand decreases.

Table 5.6: Optimal network configurations for variations of the percentage of products obtained by apheresis

Decision		**Scenario**			
		A1	**A2**	**A3**	**A4**
	Percentage of RBC from apheresis	0%	25%	0%	25%
	Percentage of Platelets from apheresis	0%	0%	25%	25%
Collection centers	Number	10	6	10	6
	Number of capacity packages required WB	69	53	69	53
	Apheresis RBC equipment	1	18	1	18
	Apheresis platelets equipment	0	0	5	6
Production centers	Number	5	4	5	4
	Number of capacity packages required WB	64	64	64	64
Distribution centers	Number	13	13	13	13
	Number of capacity packages required	112	111	112	112
Average number of donors required	Triplex bag (thousand)	252	100	327	178
	Quadruple bag – Alt. A (thousand)	365	365	291	290
	Quadruple bag – Alt. B (thousand)	45	45	45	45
	RBCs by apheresis (thousand)	2	78	1	76
	Platelets by apheresis (thousand)	0	0	7	7
Average total donors (thousand)		665	588	672	598
Average stockouts (thousand)		0	0.2	0.1	0.2
Average cost ($ million)		$34.60	$39.00	$36.90	$41.10

5.7 Discussion

This paper presents a discussion of the advantages of different configurations of the blood supply chain. In addition, a model is also presented for finding the optimal configuration of the blood supply chain that is applicable in countries with varying geographical distributions of the population. This model incorporates aspects that have not been considered in previous models such as collection and fractionation alternatives, as well as the use of apheresis products. Using a case study, we show different aspects in terms of decisions, costs and constraints that must be considered when planning the strategy for a blood system. In addition, aspects regarding the collection and blood fractionation strategy are analyzed along with the impact of the use of apheresis to replace whole blood collections.

In the collection stage, centralization can be carried out at a lower scale than production, since the location of blood collection centers is highly influenced by the distribution of the donor population. The location and capacity of collection centers depends on the donation rates of the surrounding population; for the case presented these rates are assumed to be 4% in all regions. In the centralized scenario (Scenario S7, presented in Section 5.3.6.1), the model proposes 10 collection centers along with only 5 production centers, while, in the decentralized system (Scenario S1) 17 collection centers are required to supply 15 production centers. The number of collection centers is determined by the donor population: some regions are not able to meet demand and the model must obtain the supply from other regions. However, when comparing the two scenarios S1 and S7, it is apparent that the centralized model reduces the number of collection centers by 41

From the centralization point of view, the location of blood production centers is influenced by the travel time to collection centers and distribution centers. In Scenario S7, the model proposes 5 blood production centers, where the largest is located in Bogota with a capacity of 310,000 units, while the smallest is located in Bucaramanga with a capacity of 40,000 units. In Scenario S1, the largest blood center is again located in Bogota with a capacity of 260,000 units, but there are five other blood centers, each with a capacity of 10,000 units in the solution. This is an example of how, in countries

with short travel times, centralization can be particularly attractive. For instance, in the UK, the largest blood production center is located in Filton and processes nearly 900,000 units per year (perhaps the largest blood production center in the world).

In terms of collection and fractionation strategy, the model also exploits the different alternatives. In general, the most common collection method used is the quadruple bag. However, this is not the case for all regions. In some collection centers the use of a triplex bag is higher since demand for products such as platelets and cryoprecipitate has been fulfilled from other collection centers. On the other hand, the fractionation strategy is dictated by demand requirements. The most common fractionation method is Alternative A, which results in a unit of RBCs, plasma, and platelets from a single whole blood donation (see Table 5.2) and amounts to 89% of all quadruple bags used. The remaining 11% is driven by demand for cryoprecipitate which requires the use of the alternative B for fractionation . Given this, there are a plethora of combinations to be considered when planning collection, production and distribution; these decisions are thus very complex. For this reason, advance decision-making methods such as mathematical modeling can be extremely useful since multiple aspects and combinations can be considered simultaneously.

Solutions obtained from the model must be carefully analyzed by decision-makers. Solutions are based on the information and constraints given to the model; however, in real life constraints can sometimes be relaxed. The solution approach, however, is robust in the sense that it can consider large numbers of alternatives; nevertheless; human intervention is almost always necessary to obtain a final decision that is practical and implementable.

Finally, it is important to note that the model presented here is generic and can be applied anywhere. The objective, decision variables and constraints are applicable to other systems including both, centralized and decentralized blood systems. In addition, the data used is in the model could easily be modified for other settings.

Chapter 6

Conclusions

6.1 Overview

This thesis has studied different aspects of the blood supply chain including collection, production, and location-allocation problems. The thesis is presented as a "four-paper" thesis where Chapters 2, 3, 4 and 5 each contain a separate research paper. While each paper stands alone, they build on each other: some use the same methods and they all consider related aspects of the same system. Section 6.2 summarises the overall content and the scientific contributions of each of these four papers. Sections 6.3 and 6.4 discuss the limitations of the selected techniques and methods, and identify future research directions. Finally, Section 6.5 presents additional comments from the author.

6.2 Summary of the Main Scientific Contributions

In this thesis several different models have been developed to study and improve the collection and production processes in the blood supply chain. These models employ a range of modelling approaches including discrete-event simulation, optimization, stochastic optimization and multi-objective optimization. Some of the models presented in this thesis combine more than one technique, enabling us to exploit the advantages of each approach and to generate robust decision support tools.

In Chapter 2, we have reviewed the literature on quantitative models in the blood supply chain, classifying papers according to the different stages in the supply chain. This review proposes a new taxonomy for categorizing the concepts included in the different models. In addition, the paper presents a new framework for describing the main operations management decisions at each stage of the supply chain.

In Chapter 3, we have developed an integrated simulation-optimisation model to support a range of collection and production decisions in the blood supply chain. This model is the first in the literature to consider multiple collection and fractionation alternatives while simultaneously taking the four main blood products into account. The integrated approach enabled us to incorporate important aspects such as the perishability of blood products and uncertainty in demand.

In Chapter 4, we have studied the relationship between whole blood collection and aphaeresis collection, and its impact on the cost and number of donors required. To do this, we applied an innovative integration of the augmented epsilon constraint algorithm for multi-objective optimization and the sample average approximation algorithm for stochastic optimization. This integrated approach enabled us to obtain a Pareto front in the case where demand is uncertain.

In Chapter 5, we present a location-allocation model to redesign a blood supply chain. The paper considers the benefits and drawbacks of centralised and decentralised systems, and the model is illustrated by the use of real data from Colombia. This model includes novel aspects such as multiple collection and production alternatives, joint decisions about location and capacity and uncertainty in demand. In addition, a heuristic based on the sample average approximation technique is used to solve the SAA problem which simultaneously considers multiple scenarios.

6.3 Limitations of the Research Results

We acknowledge some limitations and shortcomings of this research.

- The proposed model considered five main collection and processing alternatives: this selection was made on the basis of the information available and the system studied. However, in other systems, other collection alternatives such as plasma aphaeresis or double bag might also be available. In that case the proposed models would need to be modified to include these alternatives.
- The models presented in this thesis only consider the four main blood products (whole blood, red blood cells, plasma, and cryoprecipitate) which constitute the vast majority of products in the blood supply chain, although the operational model in Chapter 3 and the tactical model in Chapter 4 also consider ABO blood groups. However, in reality there are more than one hundred blood products and more complex blood grouping systems. None of these rarer products are considered in our models.

- The models assume that all donations are voluntary (altruistic donations). In some countries donors are paid, but we have not modelled such systems in this thesis.
- The models presented in this thesis assume reliable and available information and good data. Most of the information used in the models is normally available in blood bank information systems and the routine periodic reports produced by blood centres. However, the accuracy and availability of this information is essential for the proposed models.
- The models presented in this thesis were developed using academic licenses for both the discrete event simulation software (Anylogic) and the optimisation software (Gurobi). The licenses for commercial use of both software packages can be expensive and this can be a limitation in the application of the models. However, it is important to highlight that for both methods free packages are available on internet. This of course would require an additional effort to implement the models in these specific tools.
- Finally, the adaptation of the models proposed to other blood systems might require knowledge of modelling and programming. This could be a limitation in the extension of the proposed models to different blood systems.

6.4 Future Research in the Blood Supply Chain

The blood supply chain remains as an active topic of research given the nature and relevance around the world. At the end of each chapter the extensions of each model have been presented; however in this section, general research directions in the blood supply chain are also proposed. The application of operation management techniques is an important field of action in the research of the blood supply chain; aspects such as collaborative logistics, lean manufacturing and inventory-routing problems that have been applied in industrial supply chains can be studied and adapted in the blood supply chain. In addition, important aspects such as donor behaviour and disaster management can also play an important role in the future of the blood supply chain. We detail in this section the possibilities for applying these techniques.

Given the perishability of blood products it is necessary that collection, production and distribution centres as well as hospitals and transfusion services operate in an integrated way. Knowing real-time information of demand in hospitals helps to reduce inventories, thus also reducing wastage indicators and cost. In addition, information on the state of inventory systems at each point facilitates actions such as transhipments between inventory points, increasing the rotation of the inventory. Methods such as vendor-managed inventory can be very useful in the blood supply chain.

Approaches such as lean manufacturing are being already used in some blood systems. However, the principles of lean manufacturing can be extended to all the stages of the blood supply chain, helping to reduce waiting times in donation processes and production, inventories and lead times in distribution. The application of lean techniques would help to synchronize the whole chain and reduce the impact of variability in supply and demand.

Another aspect that might be modelled is the behaviour of donors. This would allow blood bank managers to understand donor motivations and improve campaigns. In addition, from the point of view of operations management this can also help to improve the logistics of the collection processes by using location, schedules and other strategies that incentive donation.

Finally, the blood supply chain can experience drastic changes in terms of supply and demand during disasters or catastrophes. During such events large quantities of blood are often required in a short time period. For this reason blood centres issue appeals for emergency donations; however the literature shows that in some cases the collection has not been well handled and large quantities of blood have been wasted (Sonmezoglu et al. 2005). For this reason it is necessary to include the blood supply chain in current models of disaster and humanitarian logistics.

6.5 Personal Reflections

Given the papers published from this thesis, the author of this thesis has been invited to participate as a reviewer for different journals including the *International Journal*

of Production Research, *the International Journal of Production Economics* and the *Journal of the Operational Research Society*. The papers have been focused on different aspects of the blood supply chain. The author of this thesis is pleased to become part of the academic community and collaborate with the extension of the knowledge in this area.

Appendix A

Supplement to Chapter 2

Table A.1: Taxonomic classification of the main features of quantitative models in the collection stage.

No.	Feature	No.	Feature	No.	Feature	No.	Feature
1	Type of model. (1=Scheduling; 2=Forecasting; 3=Classification; 4=Planning; 5=Comparative; 6=Evaluation; 7=Explanation).	5	Are ABO and Rh factor considered? (Y/N)	9	Methodology (S=Simulation; A=Analytical; MC=Markov chain; O=Optimisation; ST=Statistical methods; OT=Other)	13	Special periods (B=Breaks, W=Weekends, E= Emergencies, O=Other)
2	Location (M=Mobile, F=Fixed, B=Blood Centres)	6	Purpose of the study	10	Include decisions of type of bag to be used? (Y/N)	14	Type of study (A=Application; RD=Analysis with real data set; TD=Analysis with test data)
3	Size and Scope. The number refers to the data size, e.g. # of donors. (H=Hospital or demand point, BC=Blood Centre D=Donors, CP=Collection Point)	7	Are collection policies considered? (Y/N)	11	Payment for donation considered? (Y/N)		
4	Type of collection (WB =Whole Blood; A=Aphaeresis)	8	Type of donor	12	Planning horizon (O=one period, M=multi-period)		

Table A.2: Features of quantitative models in the collection stage. Blank cells indicate a lack of evidence on which to make a judgement.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cumming et al. (1976)	2	M	1BC	WB	N	Improve blood collections in order to eliminate shortages and over collection periods.	N		A	N	N	M		A
Pratt & Grindon (1982)	6	M	1CP	WB	N	Evaluate different configurations of collection points for different donor arrival rates	N	AP,WD	S	N	N	O		TD
Brennan et al. (1992)	6	M	1CP	WB	N	Evaluation of changes in configurations, work rules and staff allocation for the collection process	N	WD	S	N	N	O		A
Michaels et al. (1993)	1	M	1CP	WB	N	Analysis of different scheduling strategies in the collection process	N	AP,WD	S	N	N	O	O	RD
Melnyk et al. (1995)	3	F	1BC	WB	N	Classification of different types of donors	N	WD	ST	N	N	O		RD
James & Matthews (1996)	7		164987D	WB	O	Identify key factors in frequent donors using survival analysis	N		ST	N	N	M		RD
Glynn et al. (2003)	5	B	5BC	WB	N	Compare donor behaviour and reactive rates during a normal period and a disaster period	N		ST	N	N	M	E	RD

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Table A.2 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bosnes et al. (2005)	2	F	1BC	WB,A	N	Improve the estimation of donor arrivals for appointments	N	AP	ST	N	N	M	W	A
Custer et al. (2005)	6	M,F	5BC	WB,A	N	Evaluate the impact of different collection policies	N		S	N	N	M		RD
Godin et al. (2005)	7		1116D	WB	N	Identify the key factors to explain intention to donate blood	N		ST	N	N	O		RD
Schreiber et al. (2005)	7		7BC	WB	N	Identify key characteristics in people who have donated blood in order to establish a long term commitment	N		ST	N	N	O		RD
Sonmezoglu et al. (2005)	5	F	2BC	WB	N	Compare donation rates and reaction rates before and after the earthquake of Turkey in 1999	N	WD	ST	N	N	M	E	RD
Boppana & Chalasani (2007)	4		1BC	WB	N	Determine the optimal acquisition rate of blood during emergencies	N		MC	N	N	O	E	TD
Godin et al. (2007)	7		2231D	WB	N	Identify key factors between first time donors and repeat donors	N		ST	N	N	O		RD

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Table A.2 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Madden et al. (2007)	6	B	16BC	WB, A	N	Review impact of collection by WB or Double red cell and different deferral policies because of vCJD disease	N		S	N	N	M		RD
Yu et al. (2007)	2		20631D	WB	N	Classify and identify patterns and key factors in first time donors	N		ST	N	N	M		RD
Ghandforoush & Sen (2010)	4	M	13CP, 1BC	WB	N	Platelets collection and transport planning	N	WD	O	N	N	O		A
Lowalekar & Ravichandran (2010)	4	M	1CP, 1BC	WB	N	Platelets collection and transport planning	Y	WD	S	N	N	M		RD
Lee & Cheng (2011)	3		1BC	WB	N	Classify type of donors	N		ST	N	N	O		RD
An et al. (2011)	6		1BC	WB	N	Evaluate the impact of epidemic and crisis affecting normal donations	N		S	N	N	M	O	RD
Alfonso et al. (2012)	4	M, F	2CP	WB,A	N	Determine capacity and staff of a collection process	N	A, WD	S	N	N	O		RD
Testik et al. (2012)	3	F	1BC	WB	N	Classify donor arrival patterns	N	WD	ST	N	N	M		RD
Alfonso et al. (2013)	4	M, F	2CP	WB,A	N	Determine capacity and staff of a collection process	N	A, WD	S	N	N	O		RD

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Table A.2 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Alfonso & Xie (2013)	1	M, F	7BC, 650 CP	WB	N	Minimise the amount of product supplied by external regions by planning weekly collections.	Y		O	N	N	M		RD
Gunpinar (2013)	1	M	nCP	WB	N	Minimise distance travelled collecting blood units from remote donors	N		O	N	N	O		TD
Alfonso et al. (2014)	1	M, F	7BC, 650 CP	WB	N	Minimise the amount of product supplied by external regions by planning weekly and daily collections.	Y		O	N	N	M		RD
Jabbarzadeh et al. (2014)	4	M,F	22CP	RBC	O-	Design of an effective blood supply chain during an emergency such as earthqueake.	Y		O	N	N	M	E	RD
?	7		923D	WB	N	Understand the relevance of variables in the maintenance of donors	N		ST	N	N	M		RD

Table A.3: Taxonomic classification of the main features of quantitative models in the production stage.

No.	Feature	No.	Feature	TN	Feature
1	Size and Scope: the number refers to the size of the dataset studied. (H=Hospital or demand point; BC=Blood Centre; D=Donors;CP=Collection Point)	5	Type of model (1= Scheduling; 2= Forecasting; 3= Classification; 4=Planning; 5=Comparative; 6=Evaluation; 7=Explanation; 8=Planning)	9	Special periods (W=Weekends, E= Emergencies, O=Other)
2	Are fractionation alternatives considered?	6	ABO and Rh factor considered? (Y/N)	10	Type of inventory policy used?([R,S], [s,S], [R,s,S])
3	Products (WB=Whole Blood, RBC=Red Blood Cells, PC=Platelets, PL=Plasma, C=Cryoprecipitate)	7	Planning horizon (O: One period, M: Multi-period)	11	Are different types of demand considered? (Y/N)
4	Purpose of the study	8	Methodology (S=Simulation, A=Analytical, MC=Markov chains, O=Optimisation, ST=Statistical methods, OT=Other)	12	Type of study (A=Application; RD=Analysis with real data; TD=Analysis with test data; T=Theoretical)

Table A.4: Features of quantitative models in the production stage. Blank cells indicate a lack of evidence on which to make a judgement.

Author	1	2	3	4	5	6	7	8	9	10	11	12
Deuermeyer (1979)	1BC	Y	WB, RBC, PC	Optimal production policies with two fractionation alternatives	4	N	M	A			N	T
Katz et al. (1983)	1BC	N	PC	Evaluate a production function based on daily demand, standard deviations and inventory.	6	N	M	S	W	[R,S]	N	RD
Ledman & Groh (1984)	1BC, 60H	Y	PC	Present a methodology for platelets production planning based on a collections plan	4	Y	M	A		[R,S]	N	A
Sirelson & Brodheim (1991)	14H, 3BC	N	PC	Create profiles curves to decide inventory levels according to accepted shortage	4	N	O	S	W	[R,S]	N	RD
Haijema et al. (2007)	1BC	N	PC	Minimisation of cost through optimal production and inventory platelets problem	4	Y	M	O,S	W	[R,S]	Y	A
Haijema et al. (2009)	1BC	N	PC	Minimisation of cost through optimal production and inventory platelets problem considering breakouts	4	Y	M	O,S	W,O	[R,S]	N	A

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Table A.4 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12
van Dijk et al. (2009)	1BC	N	PC	Minimisation of cost through optimal production and inventory of platelets and what-if analysis under changes in different parameters: shelf life, compatibilities, crossmatch ratio.	4	Y	M	O,S	W	[R,S]	Y	A
Baesler et al. (2011)	1BC	Y	RBC,PL,PC	Analysis of internal capacity of a blood processing centre. Definition of policies to increase capacity.	6	N	M	S			N	RD

Table A.5: Taxonomic classification of the main features of quantitative models in the inventory stage.

No.	Feature	No.	Feature	No.	Feature	No.	Feature
1	Size and Scope: numbers indicate size of dataset (H= hospital; BC= blood centre; BB = hospital blood bank)	5	Purpose of the study	9	Crossmatch ratio included? (Y/N)	13	Methodology (S=Simulation; A=Analytical; MC= Markov chains; O= Optimisation, ST= Statistical methods, OT=Other)
2	Products (WB= whole blood; RBC= Red Blood Cells, PC= Platelets, PL=Plasma, C=Cryoprecipitate, FRBC=Frozen RBC)	6	Issuing policy (F= FIFO, L=LIFO, R=Random)	10	Crossmatch release period included? (Y/N)	14	Type of study (A=Application; RD= Analysis with real data; TD= Analysis with test data; T=Theoretical)
3	ABO and Rh factor considered? (Y/N)	7	Shortages allowed? (Y/N)	11	Emergency orders included? (Y/N)		
4	Type of Policy (NS=Not specified; [s,S],[s,Q], [R,S],[R,Qo], EWA, OIR)	8	Outdating indicators considered? (Y/N)	12	Planning horizon (O= One period, M= Multi-period)		

Table A.6: Features of quantitative models in the inventory stage. Blank cells indicate a lack of evidence on which to make a judgement.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Elston & Pickrel (1963)	1BB	RBC	Y	[R,S]	Simulation model to improve indicators such as inventory level, percentage of expiration, age of blood and shortages	F	Y	Y	N	N	N	M	S	RD
Jennings (1968)	1BB	WB	Y	[s,Q]	Presentation of trade-off curves of shortages and outdates to evaluate changes in policies and parameters	F	Y	Y	Y	Y	Y	M	S	RD
Pegels & Jelmert (1970)	1H	WB	N	NS	Evaluate the impact of two different issuing policies on blood inventory	F,L	Y	N	N	N	N	M	MC	TD
Pierskalla & Roach (1972)	1H	WB	N	NS	Evaluation of FIFO and LIFO policies for 3 different objectives	F,L	Y	Y	N	N	N	M	A	T, TD
Frankfurter et al. (1974)	1BC, 54 H	WB	Y	NS	Forecast inventory levels based on forecasting models of expiration, collections and transfusions		N	N	N	N	N	M	ST	A
Brodheim et al. (1975)	1H	WB	N	[R,Q]	Evaluation of inventory and distribution policies	F	Y	Y	N	N	N	M	MC	T

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cohen & Pierskalla (1975)	1H, 1BC	WB	N	[R,S]	Evaluation of inventory system under different ordering policies and crossmatch release period	F,L	Y	Y	Y	Y	Y	M	S	RD
Mole (1975)	1H	WB	N	[R,S]	To determine relationship between shortages and outdates.	F	Y	Y	N	N	N	M	MC	T
Cohen (1976)	1H	WB	N	[R,S]	Optimal ordering policies considering aspects such as demand, supply, perishability, issuing, ordering, return, backlogging.	F	N	Y	N	N	N	M	A	T
Nahmias & Pierskalla (1976)	1H	RBC, FRBC	N	[R,Qo]	Optimal ordering policies considering both perishable and non- perishable inventory to meet demand.	F	Y	Y	N	N	N	M	A	T
Vrat & Khan (1976)	1BC	RBC	Y	[R,S]	Definition of the optimal inventory in days according to accepted shortage and outdating rates.		Y	Y	N	N	Y	M	S	RD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Brodheim et al. (1976)	9H	RBC	Y	[R,S]	Profile curves to decide inventory levels based on shortage, and mean demand.	NS	Y	Y	N	N	N	M	S	A
Chazan & Gal (1977)	1BC	RBC	N	[R,S]	To compute age distribution and shortage rates.	F	Y	Y	N	N	N	M	A	T
Cumming et al. (1977)	1Blood REgion	FRBC	N	[s,S]	Analysis of the use of frozen RBC based on average inventory level of fresh blood, average inventory level of FRBC, percentage waste, average age and cost.	NS	N	Y	N	N	N	M	S	RD
Pegels et al. (1977)	1Blood Region	RBC, FRBC	N	NS	Evaluation of four alternatives to improve the blood supply chain through indicators such as inventory level, average age at transfusions, outdating and annual operating cost	F	N	Y	N	N	N	M	A	RD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cohen & Pierskalla (1979)	1BC	RBC	N	[R,S]	Definition of target inventory levels from single equation based on demand, crossmatch ratio and release period.	F	Y	Y	Y	Y	N	O	ST,A, S	RD
Britten & Geurtze (1979)	2BC, 27 H	WB	N	NS	Presentation of benefits of implementing a rotation policy to decrease the outdating rate.	NS	N	Y	Y	Y	Y	M	OT	RD
Kendall & Lee (1980)	3 H	RBC	N	NS	Multicriteria optimisation model to support redistribution of inventories in a region.	F	Y	Y	Y	Y	Y	O	O	RD
Friedman et al. (1982)	1BB	RBC	Y	[s,S]	Evaluation of two strategies, reduction of inventories distinct to O type and extension of shelf life.	NS	Y	Y	Y	Y	N	M	S	RD
Cohen et al. (1983)	1BC	RBC	N	[R,S]	Definition of target inventory levels from single equation based on demand, crossmatch ratio and release period considering modifications in the shelf life of blood.	F	Y	Y	Y	Y	N	O	ST,A, S	RD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Critchfield et al. (1985)	1BC	PC	N	NS	Evaluation of time series method to forecast the use of platelets	NS	N	N	N	N	N	M	ST	RD
Sapountzis (1985)	1H	RBC	Y	[R,S]	Development of a characteristic curve to calculate outdating probabilities for each blood type in a hospital.	R	N	Y	Y	Y	N	M	A	RD
Jagannathan & Sen (1991)	1H	RBC	N	[R,S]	Analytical equations to calculate shortages and outdating rates, based on parameters known such as crossmatch ratio and release period.	F	Y	Y	Y	Y	N	O	A	T, DT
Goh et al. (1993)	1H	RBC	N	NS	Evaluation of two policies for supplying demand in a two-stage inventory system.	F	Y	Y	N	N	N	O	QT	RD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Omosigho (2002)	1H	RBC	N	[R,S]	Development of an equation to calculate the probability of use of a unit for perishable inventory. In case of blood this probability can be assumed as crossmatch ratio	F	N	Y	N	N	N	M	A	TD
Pereira (2005)	1H	RBC	N	NS	Evaluation of the impact of a Type and Screen policy in the performance of the blood supply chain.	F	Y	Y	Y	Y	N	M	S	RD
Kopach et al. (2008)	1H	RBC	N	NS	Minimisation of a cost function composed of different costs such as procurement, holding, outdating, shortage, low service and change in supplying policies. The model also considers two types of demand.	F	Y	Y	N	N	N	M	QT	RD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Erickson et al. (2008)	1H	FRBC	N	[s,Q]	Forecasting model and decision rules to manage possible shortages during disaster situations		Y	N	N	N	Y	M	OT	A
Kamp et al. (2010)	Ger-many	RBC	N	NS	Strategic model to evaluate system behaviour and blood availability under pandemic scenarios	NS	Y	N	N	N	Y	M	S	RD
Fontaine et al. (2010)	1BC	RBC	Y	[R,S]	Measure the impact of different shelf lifes in inventory availability and outdate rates.	F	Y	Y	N	N	N	Y	S	RD
Blake et al. (2010)	9H	PC	N	[r,s,S]	Easy methodology based on accepted service levels to define the inventory levels of platelets, minimising shortages and outdating rates	F	Y	Y	N	N	N	M	A	A

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Zhou, Leung & Pierskalla (2011)	1H	PC	N	[R,S]	Optimal policies for 3 periods in the platelets inventory problem and two kinds of ordering processes. The objective of the model is the minimisation of total cost, which is composed by shortage cost and outdate cost	NS	Y	Y	N	N	Y	M	A	RD
Li & Liao (2012)	1BC, nH	RBC	N	[s,S]	Estimation of key parameters in blood supply chain design such as issuing policies, maximum and minimum inventories and donor arrival rate.	F	Y	Y	N	N	N	O	O, OT	RD
Duan & Liao (2013)	1BC, 3H	PC	N	[R,S], EWA, OIR	Minimisation of outdating rates according to ordering policies based on the age of the inventory	F	Y	Y	N	N	N	M	S,O	TD

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Gunpinar (2013)*	1BC,1H	RBC, PC	N	[R,Qo]	Minimise total cost: purchase cost + holding cost + wastage cost + outdate cost	F	Y	Y	Y	Y	N	M	O	RD,
Silva et al. (2013)	1BC	RBC, PC	N	NS	Application of automatic SARIMA models to forecasting demand of blood products as well as arrivals of donors.	NS	N	N	N	N	N	M	ST	RD
Telles et al. (2013)	1BC	RBC, PC, PL	Y	[s,S]	Basic inventory model to blood products. However blood is treated as a normal product since special features are not considered.	NS		N	N	N	N	O	OT	RD
Duan & Liao (2014)	1BC,1H	RBC	Y	OIR	Evaluation of inventory planning using compatibilities and three scenarios of maximum shelf life	F	Y	Y	Y	N	N	M	S,O	TD
Blake & Hardy (2014)	10BC	RBC	Y	[R,s,S]	Simulation framework to define inventory targets optimising outdates, shortages and normal and emergency orders	F	Y	Y	N	N	Y	Y	S,O	A

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Table A.6 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Gunpinar & Centeno (2015)	1BC,nH	RBC	N	[R,Qo]	Minimise total cost: purchase cost + holding cost + outdate cost	NS	Y	Y	N	N	N	M	O	RD

Table A.7: Taxonomic classification of the main features of quantitative models in the distribution stage.

No.	Feature	No.	Feature	No.	Feature	No.	Feature
1	Type of model (1= Scheduling; 2= Forecasting; 3= Classification; 4=Planning; 5=Comparative; 6=Evaluation; 7=Explanation; 8=Planning)	5	Substitute products (compatibilities) considered? (Y/N)	9	Allocation decisions? (Y/N)	13	Pick and delivery - interchange of blood products? (Y/N)
2	Size and Scope. The number denotes the size of the dataset. (H=Hospital; BC=Blood Centre; DP=Demand point (generic))	6	Returns allowed? (Y/N/NS)	10	Routing? (Y/N)	14	Planning horizon (O= One period, M: Multiperiod)
3	Products (NS = not stated; O=Other (generic); WB= whole blood; RBC= Red Blood Cells, PC= Platelets, PL=Plasma, C=Cryoprecipitate, FRBC=Frozen RBC)	7	Purpose of the study	11	Time windows constraints? (Y/N)	15	Methodology (S=Simulation; A=Analytical; MC= Markov chains, O=Optimisation; ST= Statistical methods; OT= Other)
”4	ABO and Rh factor considered? (Y/N)	8	Location decisions? (Y/N)	12	Distance indicator? (Y/N)	16	Type of study (A= Application; RD= Analysis with real data; TD= Analysis with test data; T=Theoretical)”

Table A.8: Features of quantitative models in the distribution stage. Blank cells indicate a lack of evidence on which to make a judgement.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Yahnke et al. (1973)	6	1BC,	RBC	Y	N	Y	Present and evaluate a new indicator called Effective Outdate Rate which is based on the real impact of return old blood units.	N	N	N	N	N	Y	M	MC	RD
Dumas & Rabinowitz (1977)	6	1 H	WB, RBC	Y	Y	Y	Evaluations of the impact of both inventory policies, double crossmatching and substitute products.	N	N	N	N	N	N	M	S	TD
Prastacos (1978)	6	1BC, nH	WB	N	N	Y	Presentation of two myopic policies, rotation and retention to allocate inventory in hospitals.	N	Y	N	N	N	N	O	A	A
Or & Pierskalla (1979)	8	3BC, 117H	WB	N	N	N	Location of blood centres and allocation of hospitals as well as two solution algorithms.	Y	Y	Y	N	Y	N	O	O	RD
Brodheim & Prastacos (1979)	4	1BC, 34H	WB	Y	N	Y	Pre-schedule deliveries using inventory rotation. A fixed quantity of "old blood" is returned to the blood centre to be redistributed.	N	Y	N	N	N	Y	O	S	A

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Table A.8 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Prastacos & Brodheim (1980)	8	1BC, 38H	WB	Y	N	Y	Model to allocate blood inventory including two different policies such as rotation and retention according to the age of the blood	N	Y	N	N	N	Y	M	O	A
Cerveny (1980)	6	2BC	WB	N	N	N	Heuristic procedure to determine the location of collection points	Y	N	N	N	Y	N	O	O	A
Prastacos (1981)	8	1BC, nH	WB	N	N	Y	Analytical equations to evaluate myopic and optimal policies to allocate inventory among hospitals	N	Y	N	N	N	N	M	A	TD
Gregor et al. (1982)	6	1BC, 83H	RBC	Y	N	Y	Simulation model to decrease number of emergency orders, response time, postposing surgeries and cost.	N	N	Y	Y	Y	N	M	S	RD
Sapountzis (1984)	4	1BC, 68H	WB, RBC	Y	N	N	Optimisation model to reduce the outdating rates based on activity level of each hospital and inventory allocation	N	Y	N	N	N	N	O	O	A

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Table A.8 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Federgruen et al. (1986)	4	75DP	O	N	N	Y	Two models for general allocation and routing inventory problems: minimise shortage, transport and outdate costs	N	Y	Y	N	Y	N	O	O	TD
Price & Turcotte (1986)	6	1BC	RBC	N	N	NS	Methodology to support facility location decisions using centre of gravity and multicriteria methods.	Y	N	N	N	Y	N	O	OT	RD
Sapountzis (1989)	4	1BC, 68 H	WB, RBC	Y	N	N	Minimisation of outdating rates based on activity level of each hospital and inventory allocation considering stochastic demands	N	Y	N	N	N	N	O	O	A
Jacobs et al. (1996)	6	4BC	WB	N	N	N	To evaluate location alternatives and decisions such as allocation of donors to collection points, allocation of collection points to blood centres and quantities of blood to be collected	Y	Y	N	N	Y	N	M	O	A

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Table A.8 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Sahin et al. (2007)	6	23BC	WB	N	N	N	To support decisions on location and allocation in Turkey minimising the weighted distance and blood stations	Y	Y	N	N	Y	Y	O	O	RD
Sivakumar et al. (2008)	4	7BC	NS	N	N	NS	Combination of VRP and AHP methodologies for an allocation-routing problem in a blood supply chain in India	N	Y	Y	N	Y	Y	M	O	TD,RD
Hemmelmayr et al. (2009)	1	1BC, 55H	WB	N	N	N	Introduction of vendor inventory management. The model proposes the assignation of hospital to routes planned by the blood bank considering stationary demand and replenishing quantities defined by the blood centre	N	N	Y	Y	Y	N	M	O	RD
Çetin & Sarul (2009)	4	3BC, 25H	NS	N	N	N	Minimisation of the total fixed cost of locating blood banks, total distance between hospitals and blood banks and	Y	Y	N	N	Y	N	O	O	TD

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Table A.8 – continued from previous page

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Hemmelmayr et al. (2010)	1	1BC, 55H	WB	Y	N	N	Stochastic demands and different alternatives to supply emergencies	N	N	Y	Y	Y	N	M	O	RD
Banthao & Jittarnai (2012)	4	22BC, 93H	NS	N	N	N	Minimisation cost composed by fixed cost, and ordinary and emergencies costs	Y	Y	N	N	Y	N	O	O	RD

Table A.9: Taxonomic classification of the main features of integrated quantitative models.

No.	Feature	No.	Feature	No.	Feature	No.	Feature
1	Echelons included (C= Collection; P= Production, I= Inventory, D= Distribution)	5	Fractionation (Y/N)	9	Distribution features studied	13	Methodology (S=Simulation; A=Analytical; MC= Markov chain; O= Optimisation ; ST= Statistical methods; OT= Other)
2	Size and Scope (H= Hospital or demand point; BC= Blood Centre; D=Donors; CP= Collection Point; N=Nodes)	6	Collection features studied	10	Objective(s)	14	Transhipment accepted? (Y/N)
3	Products (WB= Whole blood; RBC=Red blood cells; PC= Platelets; PL= Plasma; C=Cryoprecipitate; O= Other)	7	Production features studied	11	Indicators	15	Planning horizon (O= One period, M= Multi-period)
4	Are ABO and Rh factor considered? (Y/N)	8	Inventory features studied	12	Crossmatch? (Y/N)	16	Type of study (A= Application; RD= Analysis with real data; TD: Analysis with test data)

Table A.10: Features of integrated quantitative models literature in the blood supply chain. Blank cells indicate a lack of evidence on which to make a judgement.

Author	1	2	3	4	5	6	7	8	9
Kendall (1980)	C,I,D	1BC	WB	N	N	Collection goals		[R,S]	Not specified
Page (1980*a*)	I,D	1BC, 9H	WB	Y	N			Forecast inventory levels; No specification of policies	Allocation of inventory; Reallocation of old units from demand points with high probabilities of transfusion
Rytilä & Spens (2006)	I,D	1BC, 1H	RBC, PL, PC	Y	N				Crossmatch ratio; Compatibilities; Time release period; returns
Katsaliaki & Brailsford (2007)	C,P,I,D	1BC, 1H	RBC	Y	N			[s,Q]	Crossmatch ratio; Crossmatch release period Mismatching

Continued on next page

Table A.10 – continued from previous page

Author	1	2	3	4	5	6	7	8	9
Yegül (2007)	C,I,D	2CP, 1BC, 49H,	RBC	Y	N			[R,S]	Transhipments allowed; Heuristic rule for issuing; Mismatching policies; Crossmatch ratio; Crossmatch release period
Lang (2010)	I,D	1BC, nH	RBC	Y	N			[R,S]	FIFO Substitution allowed Transhipment allowed
Delen et al. (2011)	I,D	81 BC	RBC PL PC O	N	N				Not specified

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Table A.10 – continued from previous page

Author	1	2	3	4	5	6	7	8	9
Lowalekar & Ravichandran (2011)	C,P,I	1CP, 1BC	WB, RBC, PC, PL	N	Y	Modified R,Q; Modified R, S	FR*		
Nagurney & Masoumi (2012)	C,P,I,D	5N	WB, RBC	N	N				Not specified
Nagurney et al. (2012)	C,P,I,D		WB, RBC	N	N				Not specified
Blake et al. (2013)	I,D	2BC, 146H	RBC	Y	N	Poisson distribution to represent collection rates		[R,s,S]	FIFO Substitution allowed Transhipment allowed Demand points with different sizes

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Table A.10 – continued from previous page

Author	1	2	3	4	5	6	7	8	9
Abdulwahab & Wahab (2014)	C,I	1CP-1BB	PL	Y	N	No included, represented by expected value in donations		Up-to policies	Mismatching policies Issuing policies
Baesler et al. (2014)	C,P,I,D	1BC	RBC, PL, PC	Y	Y	Stochastic collections		Reorder point-Extra Donations-Optimal Inventory	
Simonetti et al. (2014)	C,I,D	1CP, 1BC	RBC	Y	N				Issuing policies Mismatching policies

Table A.11: Features of integrated quantitative models literature in the blood supply chain. Blank cells indicate a lack of evidence on which to make a judgement.

Author	10	11	12	13	14	15	16
Kendall (1980)	Evaluate the best alternative for blood bank planning under several objectives	Cost, Shortages, Outdates, Inventory, Collections	N	A	N	O	A
Page (1980*a*)	Evaluate three strategies, heuristic procedures for allocation, forecasting of inventory levels and recycling of old blood units.	Inventory cost per transfused unit, which considers wastages and shortage costs	Y	S	Y	M	RD
Rytilä & Spens (2006)	Evaluation of eleven scenarios such as variation on inventory, issuing policies and crossmatch ratio.	Outdating rate; Outdating cost; Back order cost; Back order rate; Savings	Y	S	Y	M	A

Continued on next page

Table A.11 – continued from previous page

Author	10	11	12	13	14	15	16
Katsaliaki & Brailsford (2007)	Simulation model to evaluate and generate improvement proposals. The model includes the main features of the blood supply chain	Number of outdates; Number of shortages; Number of mismatches; Number of orders (routine, ad-hoc, emergency)	Y	S	N	M	RD
Yegül (2007)	Evaluate scenarios and policies for the new structure of the Turkish blood supply chain	Inventory levels; Shortage rate; Outdating rate; Mismatching rate	Y	S	Y	M	RD
Lang (2010)	Simulation optimisation model to evaluate the impact of using transhipments and substitute products	A weighted function of the number of occurred shortages and the number of transhipments	N	S,O	Y	M	TD
Delen et al. (2011)	Application of several OR methodologies to manage the blood supply chain.	Not specified	N	O, OT	Y	M	A

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Table A.11 – continued from previous page

Author	10	11	12	13	14	15	16
Lowalekar & Ravichandran (2011)	Generate profile curves to support the decision maker to manage collection and fractionation policies.	Wastage rate; Fill rate; Annual cost	N	S	N	M	RD
Nagurney & Masoumi (2012)	Minimization of cost and risk of a blood supply chain under network theory.	Total discard cost of waste/loss; Total blood supply shortage cost Total discard cost of outdated blood Risk	N	O	N	O	DT
Nagurney et al. (2012)	Similar to the above. The difference is the inclusion of discard cost along the supply chain and the consideration of arc capacities as decision variables.	Total discard cost of waste/loss; Total shortage cost; Total discard cost of outdated blood; Risk	N	O	N	O	DT
Blake et al. (2013)	Analysis of the impact over the blood supply chain indicators of reducing the shelf life of red blood cells	Outdate rate Shortage rate Emergency orders	N	S	Y	M	RD

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Table A.11 – continued from previous page

Author	10	11	12	13	14	15	16
Abdulwahab & Wahab (2014)	To propose an approximate dynamic program for inventory planning in a platelets blood bank	Shortage rates Outdating rates Inventory levels Awards by meeting demand	N	O	N	M	RD
Baesler et al. (2014)	Develop inventory policies for emergency collection campaigns. Estimation of reorder points to minimise wastage and outdating rates as well as decision rule about when to start an extra collection campaign.	Total production Units Outdated Unsatisfied demand	N	S	N	M	RD
Simonetti et al. (2014)	Evaluation of three different issuing policies considering indicators of availability and shortages.	Stock levels Average daily number of units Annual average daily of number of units by type	N	S	N	M	RD

Appendix B

Supplement to Chapter 3

Table B.1: Values of set elements used in the example model.

Day	Donors	RBC	Plasma	Cryop.*	Platelets
Sunday	Lognormal(90.725,45.635,0)	Gamma(3.6582,19.145,0)	0.5493*Weibull(1.571,43.243,0)	Actual	Weibull(2.6342,44.874,0)
Monday	Triangular(0,172.01,116)	triangular(0,132,250.37)	1.0864*Weibull(1.571,43.243,0)	Actual	Gamma(4.9766,9.2618,0)
Tuesday	Gamma(14.908,7.406, 0)	Gamma(10.466,12.198,0)	1.0327*Weibull(1.571,43.243,0)	Actual	Gamma(6.9138,8.1944,0)
Wednesday	Gamma(12.853,9.96,0)	Weibull(3.457,132.19,0)	1.2364*Weibull(1.571,43.243,0)	Actual	Gamma(4.7146,9.317,0)
Thursday	Weibull(3.3489,145.3,0)	Gamma(10.277,11.586,0)	1.1006*Weibull(1.571,43.243,0)	Actual	Gamma(5.7338,8.06,0)
Friday	Gamma(10.47,9.8342,0)	Gamma(13.781,11.601,0)	1.3835*Weibull(1.571,43.243,0)	Actual	Gamma(4.8136,8.7179,0)
Saturday	Weibull(1.8248,57.18,0)	Gamma(6.6579,10.279,0)	0.6111*Weibull(1.571,43.243,0)	Actual	Beta(1.5186,1.2625,0,68.669)

*Cryoprecipitate

Table B.2: Blood products obtained in each process.

Index	Collection Alternatives	Products required	Horizon planning (days)	Blood groups	Set of values for the shelf life of platelets (days)	Platelets production method
	Set K	Set J	Set T	Set I	Set S	Set P
0	Triplex bag	RBCs O+ Fractionation	0	O+	0	Fractionation
1	Quadruple bag – Alt. A	RBCs A+ Fractionation	1	A+	1	Aphaeresis
2	Quadruple bag – Alt. B	RBCs B+ Fractionation	2	B+	2	
3	RBC by aphaeresis	RBCs O- Fractionation	3	O-	3	
4	Platelets by aphaeresis	RBCs A- Fractionation	4	A-	4	
5		RBCs B- Fractionation	5	B-	5	
6		RBCs AB+ Fractionation	6	AB+		
7		RBCs AB- Fractionation		AB-		
8		RBCs O+ Aphaeresis				
9		RBCs A+ Aphaeresis				
10		RBCs B+ Aphaeresis				
11		RBCs O- Aphaeresis				
12		RBCs A- Aphaeresis				
13		RBCs B- Aphaeresis				
14		RBCs AB+ Aphaeresis				
15		RBCs AB- Aphaeresis				
16		Platelets Fractionation				
17		Platelets Aphaeresis				
18		Plasma				
19		Cryoprecipitate				

Appendix C

Supplement to Chapter 4

C.1 Compatibility Tables

Table C.1: Red blood cells compatibility

		Patient							
	ABO Rh	A-	A+	AB-	AB+	B-	B+	O-	O+
Donor	A-	x	x	x	x				
	A+		x		x				
	AB-			x	x				
	AB+				x				
	B-			x	x	x	x		
	B+				x		x		
	O-	x	x	x	x	x	x	x	x
	O+		x		x		x		x

Table C.2: Plasma and cryoprecipitate compatibility

		Patient			
	ABO	A	AB	B	O
Donor	A	x			x
	AB	x	x	x	x
	B			x	x
	O				x

Table C.3: Platelets compatibility

		Patient	
		Rh-	Rh+
Donor	Rh-	x	x
	Rh+		x

C.2 Formulation of the Augmented Epsilon-Constraint Algorithm (adapted from Mavrotas (2009))

A multi-objective optimization problem with k objectives is usually expressed as follows: find:

$$x = [x_1, x_2, ..., x_n], \tag{C.1}$$

that minimises

$$F(x) = [F_1(x), F_2(x), ..., F_n(x)], \tag{C.2}$$

subject to:

$$g_j(x) \leq 0, \quad \forall j = 1, 2, ..., m. \tag{C.3}$$

,

In order to convert the multi-objective model defined in (C.1) – (C.3) into a mono-objective model using the idea of the augmented ε-constraint algorithm, the formulation is modified as follows:

Find the same vector expressed in (C.1) that minimises:

$$F(x) = F_1(x) - \beta \sum_{i=2}^{k} \frac{w_i}{r_i}, \tag{C.4}$$

subject to:

$$F_i(x) + w_i = \varepsilon \quad \forall i = 2, 3, ..., k, \tag{C.5}$$

$$g_j(x) \leq 0, \quad \forall j = 1, 2, ..., m. \tag{C.6}$$

,

In this formulation w represents a surplus variable for each epsilon constraint. These variables are added to the objective function with very low coefficients (β) in such a manner that does not distort the objective function but also improves the function associated with the epsilon constraint. Finally, the parameter r_i is the range of the values for each objective function $F_i(x), i = 2, \ldots, k$. These coefficients work as a normalization operator in order to sum the objective functions.

In order to find an optimal Pareto solution, a value for ε should be chosen, then the optimization problem is solved. This procedure is repeated for different values of ε to find new solutions that belong to the Pareto front.

C.3 Sample Average Approximation Algorithm

(as described in Santoso et al. (2005) **Step 1:** Generate M independent samples, each of size N:(ξ_j^1,...,ξ_j^N), for j = 1, ..., M. For every sample solve the corresponding SAA (equation 4.23). Let v_N^j and $\hat{y}_N^j$, for j = 1, ..., M, represent the optimal value and optimal solution respectively.

Step 2: Calculate the following statistical indicators:

$$\bar{v}_{N,M} = \frac{1}{M}\sum_{j=1}^{M} v_N^j \tag{C.7}$$

,

$$\sigma^2_{\bar{v}_{N,M}} = \frac{1}{M(M-1)}\sum_{j=1}^{M}(v_N^j - \bar{v}_{N,M})^2 \tag{C.8}$$

,

Step 3: Select a solution $\bar{y} \in Y$ to the original problem, using one of the $\hat{y}_N^j$ solutions already obtained. In our case the solution selected is the one with the best objective value. Estimate the true objective value $f(\bar{y})$ by using the expression:

$$\tilde{f}_{N'}(\bar{y}) = c^T\bar{y} + \frac{1}{N'}\sum_{n=1}^{N'} Q(\bar{y}, \xi^n) \tag{C.9}$$

where (ξ^1,...,$\xi^{N'}$) is an independent sample of size N'. It is expected that N' is considerably larger than the sample size N used in step 1. Obtain the variance as follows:

$$\sigma^2_{N'}(\bar{y}) = \frac{1}{N'(N'-1)}\sum_{n=1}^{N'}(c^T\bar{y} + Q(\bar{y}, \xi^N) - \tilde{f}_{N'}(\bar{y}))^2 \tag{C.10}$$

Step 4: Calculate the optimality estimator based on the results from steps 2 and 3.

$$gap_{N,M,N'} = \tilde{f}_{N'}(\bar{y}) - \bar{v}_{N,M} \tag{C.11}$$

$$\sigma^2_{gap} = \sigma^2_{N'}(\bar{y}) + \sigma^2_{\bar{v}_{N,M}} \tag{C.12}$$

,

C.4 Bender's Decomposition Algorithm

Bender's decomposition algorithm decomposes the model creating a master problem associated with the first-level variables and a set of sub-problems associated with the second level variables. When first-level variables are fixed the sub-problem is usually easy to solve. The solution of the sub-problem allows the generation of optimality cuts to be included in the master problem. The process iterates until the solution of both master and sub-problem converge. In the version presented in Santoso et al. (2005) and used in this paper, the algorithm is adapted to consider N scenarios solving one sub-problem for each scenario. The detail of the algorithm is explained as follows:

Initialization step Let $lb = -\infty$ and $ub = +\infty$, respectively and set the iteration counter $i = 0$. Let $\hat{y}$ denote the incumbent solution.

Step 1: Solve the master problem

$$lb = \min_{y,\theta} f(z) = c^T y + \theta \tag{C.13}$$

subject to:

$$y \in \mathbb{Z}_+^{|E|} \tag{C.14}$$

$$\theta \geq a_k y + b_k, \quad \forall k = 1, ..., i. \tag{C.15}$$

Step 2: For $n = 1,\ldots, N.$, solve the sub-problems (4.17) – (4.23) corresponding to the y^i and $\xi^n = (d^n)$. The problem is re-stated as follows:

$$Q(y^i, \xi^n) = \min_{y,z,s} q^T x + h^T s - \beta^T w \tag{C.16}$$

subject to:

$$\boldsymbol{E}z + s \geq d^n, \quad (\mu) \tag{C.17}$$

$$\boldsymbol{G}z \leq \boldsymbol{H}x, \quad (\tau) \tag{C.18}$$

$$\boldsymbol{N}x \leq 0, \quad (\phi) \tag{C.19}$$

$$\boldsymbol{R}x \leq \boldsymbol{M}y^i, \quad (\rho) \tag{C.20}$$

$$\boldsymbol{B}x \leq 0, \quad (\psi) \tag{C.21}$$

$$\boldsymbol{A}x + w = \varepsilon, \quad (\alpha) \tag{C.22}$$

where $\mu, \tau, \phi, \rho, \psi$ and α are the dual values for the constraints (4.18) – (4.23). The objective function value of the current solution y^i can be computed using the sub-problem objective values as follows:

$$\hat{f}_N(y^i) = c^T y^i + \frac{1}{N} \sum_{n=1}^{N} Q(y^i, \xi^n) \tag{C.23}$$

,

if $\hat{f}_N(y^i) < ub$ then $ub = \hat{f}_N(y^i)$ and $\hat{y} = y^i$.

Step 3: If $ub - lb < \delta$, where $\delta \geq 0$ is the pre-specified gap tolerance, stop and return y^i as the optimal solution and ub as the optimal objective value; otherwise proceed to Step 4.

Step 4: For each for $n = 1,\ldots, N.$, let $\mu_i^n, \tau_i^i, \phi_i^n, \rho_i^n, \psi_i^n$ and α_i^n be the optimal dual solutions for the corresponding to y^i and ξ^n solved in step 2. Compute the optimality cuts coefficients:

$$a_{i+1} = \frac{1}{N} \sum_{n=1}^{N} M \rho_i^n \tag{C.24}$$

and

$$b_{i+1} = \frac{1}{N} \sum_{n=1}^{N} (\alpha_i^n \varepsilon + d^n \mu_i^n) \tag{C.25}$$

Let $i = i+1$ and go to Step 1.

C.5 Allocation by Product

Table C.4: Red blood cells allocation

		Patient							
	ABO Rh	A-	A+	AB-	AB+	B-	B+	O-	O+
Donor	A-	4,253	374	35	5				
	A+		41,776		80				
	AB-			449	29				
	AB+				2,287				
	B-			43	9	1,025	146		
	B+				60		11,642		
	O-	376	113	8	8	179	87	8,755	369
	O+		2,287		47		628		95,898

Table C.5: Plasma allocation

		Patient			
	ABO	A	AB	B	O
Donor	A	29,621			6,177
	AB	106	1,721	173	36
	B			8,403	1,153
	O				72,968

Table C.6: Cryoprecipitate allocation

		Patient			
	ABO	A	AB	B	O
Donor	A	5,272			1,628
	AB	178	321	167	31
	B			1,463	745
	O				8,636

Table C.7: Platelets allocation

		Patient	
		Rh-	Rh+
Donor	Aphaeresis Rh-	93	107
	Aphaeresis Rh+		333
	Fractionation Rh-	9,433	533
	Fractionation Rh+		106,452

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