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Characterization and Optimization of the Pharmaceutical Supply Chain Under Uncertainty and Regulatory Conditions

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UNIVERSIDAD DE LA SABANA
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A mi familia, A mi novia, a quienes amo inmensamente

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Chapter 1

Introduction

According to the World Health Organization (WHO): "A health system includes all organizations, institutions, resources and people whose primary purpose is to improve health" [Organization 2010]. It has been shown that health systems are complex since they meet the following characteristics [Lipsitz 2012], [Kannampallil 2011]:

- Non-linearity since the results of any disturbance are not predictable
- Permanent changes because their environment changes constantly
- Interconnections that are presented between the different actors involved
- Feedback on the information that returns in some way to the system
- Uncertainties that can not be controlled by the health system
- Relationship with time since short and long term results can be differentiating factors

Therefore health systems not only are related with the main activities in the provision of services but also all those secondary or support activities that lead to the achievement of the objectives, one of them is the supplying of medicines. As one of the main objectives of healthcare systems is to guarantee the access to medicines as a human right [Hogerzeil 2006], multiple actors (such as suppliers, manufacturers, warehouses, distribution centers and providers) are involved in the movement of multiple products through multiple echelons which constitute a supply chain, specifically the pharmaceutical supply chain that has a high level of complexity because of the dynamics nature of relationship between the members as well as the uncertainty presented in different levels of decisions [Ahmadi 2018].

The main objective of the pharmaceutical supply chain is to produce medicines and create the transportation plan to distribute them [Xie 2012], this movement of medicines involves several actors as: primary manufacturers, secondary manufacturers, distribution centers and wholesalers, retailers and pharmacies and hospitals where each one of these actors have its own specifications, goals, obligations and priorities. Different challenging requirements made that the pharmaceutical supply

chain has a high level of uncertainty. Some of these elements can be summarized as follows [Singh 2016], [Zahiri 2018]:

- Product discovery
- Participation of different stakeholders
- Perishability of medicines
- Regulatory contexts and healthcare reforms
- High variability of demand
- Quality standards
- High level of costs

Supply chain management costs account for 25% to 30% of total costs in hospital expenses [Gebicki 2014]. Additionally, the costs associated with moving and handling medicines can account for 35% to 40% of the total logistics costs [McKone-Sweet 2005]. The pharmaceutical industry is one of the most challenging industries in the world, and it is estimated that medicines account for approximately 10% to 30% (sometimes as high as 60%) of global health spending [Xu 2018]. Given the inherent differences between medicines and traditional industrial products, compared to the analysis of traditional supply chains, the analysis of pharmaceutical supply chains requires special considerations. For example, some medicines and surgical supplies must be available for use at all times [James Little 2008], and medicines have strict regulatory requirements related to the length of manufacturing time, distribution, product shelf life, and the reimbursement values that can be obtained by the government or the insurer [Almarsdóttir 2005].

In some countries, health expenses can range from 7% to 10% of the total gross domestic product, and the pharmaceutical costs take up a large portion of this total, reaching approximately 10% [Priyan 2014]. According to World Health Organization (WHO) the supply of medicines is a distribution and dispensation system to the hospitalized patient. In this system medicines are prepared in pharmaceutical services in order to guarantee the quantities correspond to the required dose in a single administration and it is labeled with the name of the patient for being administrated without any subsequent preparation. Hospitals and clinics face several problems, such as the high and variable prices of medicines, physical and monetary constraints and the medicines' expiration due to their perishability. The managers of hospitals have given importance to this context in order to optimize pharmaceutical supply chain decisions, such as supplier selection, expiration dates, quantities, and supply system performance indicators [Dua 2019].

In this way, and taking into account the previous challenges, one important objective of managing a pharmaceutical supply chain is to reduce the healthcare costs without sacrificing patients service, meaning that medicines are administrated to the right patient in the right quantity in the right time and in the right condition [Uthayakumar 2013].

Given this a well managed supply chain is considered as a key for getting a competitive advantage in hospitals and in every industry, it is also important to use efficiently the information to synchronize all the activities of the echelons and operations in the supply chain. The pharmaceutical supply chain can be categorized as a unique because it has big differences with the traditional supply chains because the tight regulations, reimbursement values, prices regulated by governmental agencies, primary and secondary medicines or substitutes, difficulty to predict the life cycle of a medicine, impossibility to back-order a demand, among others.

In addition to these characteristics which make it different from other supply chains, the pharmaceutical supply chain deals also with uncertainty; for example, the demand of each medicine is uncertain and can be influenced by seasonal changes. Moreover, due to the regulatory conditions, the costs and reimbursement values can be uncertain.

Additionally the increase of the costs of services in the health sector and the welfare of patients, are two important factors to consider in the achievement of the efficiency in the pharmaceutical supply chain [Dua 2019]. A significant part of total costs in the health sector corresponds to the handling and supply of medicines that are used to meet the needs of patients. The optimization of pharmaceutical supply chain is relevant not only for its impact on the cost structure of health systems, but also on the effectiveness and efficiency of the service provided to the patient.

For this reason this thesis is focused on the study of Pharmaceutical Supply Chain Management making emphasis in one of the echelons: the hospitals, in order to optimize the supply of medicines to patients in hospitals to improve the efficiency and service level provided to the patient and improve cost management under regulatory conditions and uncertainty. In this way operations research and simulation models becomes important tools for modeling, analyzing and optimizing decisions in the chain, specifically optimization under uncertainty models, simulation and machine learning models.

Context of the study

Some chapters of this thesis take as study case an university hospital that works under the regulation of the Colombian state. In Colombia, the healthcare system is part of the social security regulated by the government and specifically by the Ministry of Health and Social Protection and the Ministry of Labor. The system is composed by three entities:

- The Government: its main function is to regulate, coordinate an control the different agencies and enterprises that belongs to healthcare sector, its representation in the health system is through the ministry of health and social welfare.
- Social and health insurers: are entities that provide health insurance coverage to the population, acting as intermediaries and managers of the resources provided by the state defined as Capitation Payment Unit (UPC in Spanish). In this level the health promoting entities (EPS in Spanish) and the occupational risk managers (ARL in Spanish) are presented.
- Healthcare providers: the institutions providers of health (IPS in Spanish), containing the hospitals, clinics, laboratories, independent health professionals (doctors, nurses and others), ambulances, among others. They directly provide the service to the users or patients and provide all the necessary resources for the recovery of health and the prevention of diseases.

The health services are divided into POS and non POS (Obligatory Health Plan and Non Obligatory Health Plan). The POS contains a basic set of services for healthcare attention which an user in the national health system can access without an additionally payment. Its main purpose is the protection of health, the prevention and cure of diseases and the supply of the medicines to patients. POS is divided into contributory scheme and subsidized regime, depending on the payment capacity of the patient but the basic services are covered in both models. Additionally, there is a list of medicines and medical procedures that belongs to the non POS program and they are not included in the POS.

Finally, there is a solidarity fund named FOSYGA (in Spanish fondo de solidaridad y garantía), that manages the resources collected to invest in health programs and manages the resources for the reimbursement policies of medical treatments and/or medicines used in hospitals. This fund works through several sub-accounts in which monthly contributions are distributed.

The Colombian health system is presented in Figure 1.1.

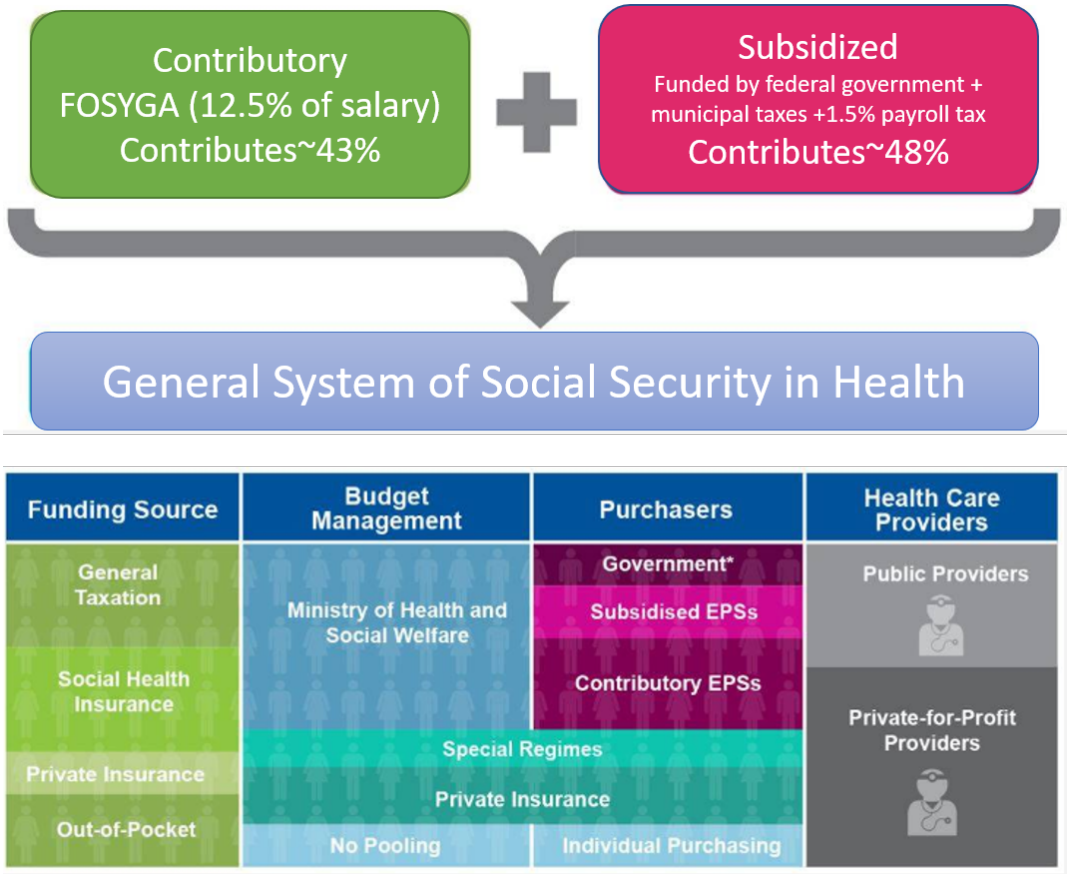

Figure 1.1: Colombian health system [QUARTERLY 2017]

Objectives

Based on the challenges and context presented above, the main objective of this thesis is to develop models to describe and optimize the pharmaceutical supply chain, making emphasis in the hospital's echelon, considering uncertainty and regulatory conditions.

To support this objective, the following secondary objectives has been defined:

- Characterize the pharmaceutical supply chain by the description of the interaction of the different echelons and their sources of uncertainty and the operational conditions.
- Develop mathematical models to optimize the pharmaceutical supply chain, making particular emphasis on the hospitalary echelon, taking into account constraints of regulatory conditions and the uncertainty associated.

- Develop models to estimate the pharmaceutical expenditure associated with chronic diseases.

- Develop models to estimate the demand of medicines taking into account factors related to seasonal epidemics.

Structure of the thesis

This thesis is organized in 7 different chapters. In Chapter 2 a systematic literature review is presented. The review is focused on quantitative methods for pharmaceutical supply chain focused on three categories of classification proposed: (i) network design, (ii) inventory models and (iii) optimization of a pharmaceutical supply chain. A taxonomy for each category is presented describing the main results obtained by the review. Finally, the main contributions of this thesis related to the literature is presented.

Chapter 3 presents a characterization and a conceptual modeling framework of the pharmaceutical supply chain dynamics by using causal loop diagrams. Based on this characterization, a simulation model based on system dynamics was build to estimate the cost of managing medicines in hospitals. Five different medicines are used to test the simulation model and contrast with the reimbursement value regulated by governmental policies to determine gaining or losses for the hospital. Finally, a sensitive analysis are presented. With the model developed decision makers in both sides (hospitals and government) can support the process of decision making by studying the interaction between the uncertainty factors and variables that affect the final cost of medicines.

Chapter 3 shows that the final cost of supply medicines to patients is not static and it is affected by different dynamics and factors related to the amount of expired medicines, adjustment costs, logistic costs, emergency purchases and shortages. Based on this 4 presents an application of simulation-optimization approach where the stochastic counterpart or sample path method is used for optimizing tactical and operative decisions in the pharmaceutical supply chain. This approach focuses on the pharmacy-hospital echelon, and it takes into account random elements related to demand, costs and the lead times of medicines. Based on this approach, two mixed integer programming (MIP) models are formulated, these models correspond to the stochastic counterpart approximating problems. The first model considers expiration dates, perishability and other important elements which are related with legal regulations as the service level required, aged-based inventory levels, unit-doses preparation and emergency purchases. The optimal policy support decisions related to the replenishment, supplier selection and the inventory management of medicines. The results of this model have been evaluated over real data and simulated scenarios. The second model is a bi-objective optimization model solved with the epsilon-constraint method. This model determines the maximum acceptable

expiration date, thereby minimizing the total amount of expired medicines.

The medicines' replenishment decisions associated to the models presented in Chapter 4 can be considered as operative or tactical. However in the management of medicines there are also strategic decisions, in this sense Chapter 5 presents models to optimize the process related to unit-doses and prescriptions management in a network of hospitals where also the location-allocation of pharmacy robots decisions are evaluated. Two mathematical models are presented, the first one a deterministic model that considers the real operational constraints of the process of preparing and distributing prescriptions and unit-doses prescriptions. The second one based a stochastic model in which the uncertainty of demand of medicines and the multi-source resilience strategy are considered to avoid the risk of centralized distribution processes in a very sensitive network managing the demand of medicines and prescriptions. The uncertainty of the demand of medicine is included by using the p-robustness approach that combines the minimization of the expected cost and the minimization of the worst case or regret.

One of the critical issues in organizations is the financial and budget planning, Chapters 3, 4 and 5 show the impact of managing medicines in the budget of hospitals. For this reason the estimation of the expenditure of medicines could support the planning process in hospitals. For this reason in Chapter 6 different models based on machine learning techniques are presented to estimate the pharmaceutical expenditure associated to a chronic disease (diabetes). Different models are tested in two different stages. In the first stage five different machine learning models were tested: generalized linear model, deep learning, random forest, gradient boosted trees and support vector machines. The first results showed that the predicted values have high variability for all the models tested. Therefore, the machine learning models were combined with additional techniques: (i) feature selection, (ii) boosting and (iii) optimized support vector machine. The results showed a reduction in the variability and improvements in the performance indicators. The second stage consists in the addition of two new variables to the data base: the Charlson index and the number of comorbidities, these variables were calculated based on the condition of each patient of the data base. With this new information the same models tested in the first stage are tested in the second stage in order to analyze the impact of the comorbidity in the performance of the machine learning models to estimate the pharmaceutical expenditure.

Another element that support the planning process in hospitals corresponds to the estimation of the medicines' demand, in this sense in Chapter 7 forecasting models based on machine learning techniques are presented to estimate the consumption of medicines within hospitals in seasonal epidemics. Two different models are applied: (i) Support Vector Machines and (ii) Neural Networks by using the data related with the demand of medicines and the seasonal epidemics of public databases in Colombia. Once the models are built and tested, different performance

measures are used to evaluate the statistical performance of both models.

Finally, the conclusions and some future works are included.

In Figure 1.2 the structure of the thesis are summarized, using the strategic, tactical and operational views of the logistics planning process.

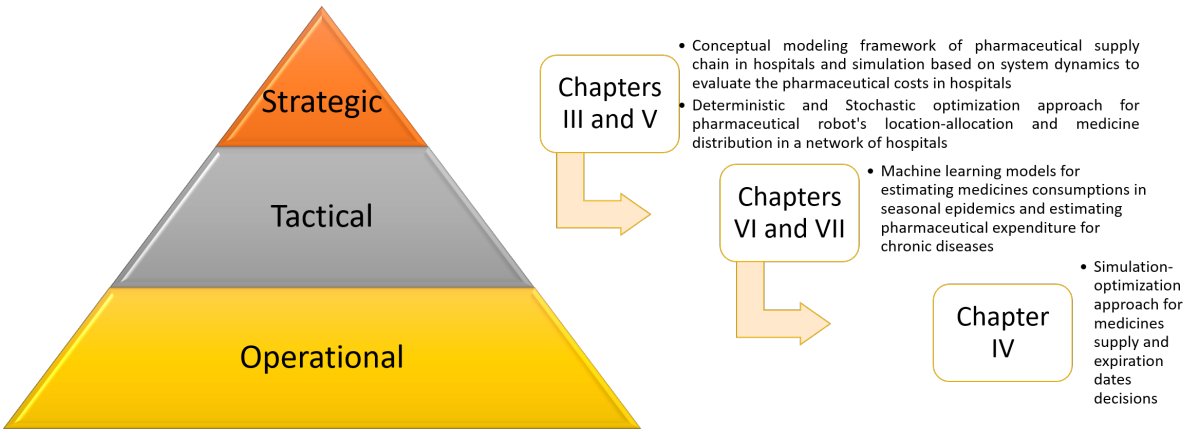

Figure 1.2: Structure of the thesis - logistics planning process

Summary of publications

The following are the publications based on this thesis.

Journal articles published:

- Carlos Franco, Edgar Alfonso-Lizarazo, Optimization under uncertainty of the pharmaceutical supply chain in hospitals, Computers Chemical Engineering, 2019, ISSN 0098-1354, https://doi.org/10.1016/j.compchemeng.2019.106689. In Press.
- Franco, C.,Alfonso-Lizarazo, E. (2017). A Structured Review of Quantitative Models of the Pharmaceutical Supply Chain. Complexity, 2017: 1-13. DOI: https://doi.org/10.1155/2017/5297406.
- Franco, C. A simulation model to evaluate pharmaceutical supply chain costs in hospitals: the case of a Colombian hospital. DARU Journal of Pharmaceutical Sciences, 2018, ISSN 2008-2231, https://doi.org/10.1007/s40199-018-0218-0. In Press.

Conferences with proceedings:

- Franco, C.,Augusto, V., Garaix, T. Alfonso-Lizarazo, E. Bourdelin, M. bontemps, H. Strategic territorial deployment of hospital pharmacy robots using a stochastic p-robust optimization approach. Proceedings IEEE International Conference on Automation Science and Engineering (IEEE CASE 2018) Munich, Germany.

Conferences without proceedings:

- Franco C., Alfonso-Lizarazo, E. Integrated analysis for characterization and optimization of pharmaceutical supply chain in a Colombian hospital. Presented in the 29th POMS conference. Houston, United States.

Additionally, the following award was obtained:

- The Emerging Economies Doctoral Student Award (EEDSA) 2018, given by the Production and Operations Management Society (POMS), Houston - United States.

Chapter 2

Structured review of quantitative models of the pharmaceutical supply chain

Contents

The aim of this chapter is to identify and provide a structured overview of quantitative models in the pharmaceutical supply chain, a subject not exhaustively studied in the previous reviews on healthcare logistics related mostly to quantitative models in healthcare or logistics studies in hospitals. The models are classified into three categories: network design, inventory models, and optimization of a pharmaceutical supply chain. A taxonomy for each category is shown describing the principal features of each echelon included in the review. Finally, the main contribution of this thesis with respect to the literature are presented.

2.1 Introduction

One of the objectives of a healthcare system is to guarantee access to medicines as a basic human right [Ahmadiani 2016]. The pharmaceutical supply chain must provide the correct medicines in an adequate condition, to the right customer, at the right time and place and at a minimum cost [Rankin 1999]. The high level of complexity in the healthcare sector is represented in the interactions between

the various echelons in the chain, including vendors, manufacturers, distributors, wholesalers and providers [Burns 2002][Chung 2016].

A typical configuration of a pharmaceutical supply chain includes a group of manufacturers which can be divided into five categories: multinational, generic manufacturers, local companies, contract manufacturers and biotechnological companies [Sousa 2011]. Also included are a group of purchasers, including wholesalers and distributors, and a group of providers including hospitals, clinics and pharmacies [Burns 2002]. The activities of a pharmaceutical supply chain involve the flow and transformation of medicines from raw materials through to the end users; in addition, the associated information flows through the relationships in the supply chain to achieve a sustainable competitive advantage [Handfield 1999]. An illustrative example of a typical configuration of the pharmaceutical supply chain is presented in Figure 2.1.

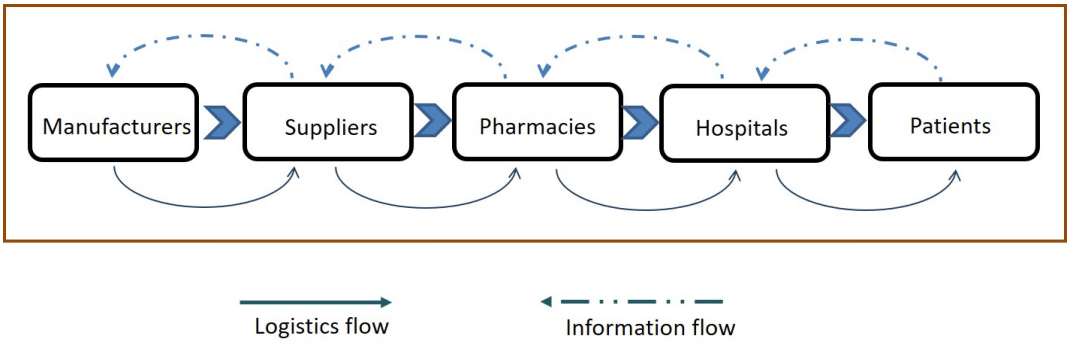

Figure 2.1: Typical configuration of a pharmaceutical supply chain, adapted from [Sousa 2011]

In addition to the contribution of health services, the pharmaceutical supply chain is an important contributor to the healthcare system [Narayana 2014]. The pharmaceutical industry is one of the most challenging industries in the world, since it is estimated that medicines consume about 20% to 30% of global health spending [Organization 2010]. However, pharmaceutical supply chain management is more difficult than typical applications within industrial companies, since medicines and surgical supplies must be available for use at all times [James Little 2008].

It has been shown that the appropriate management of medicines and pharmaceutical products is directly related to the ability of a country to address public health concerns; it has also been identified that the management of pharmaceutical supplies is one of the most important managerial issues in healthcare industries [Aptel 2001].

According to [Uthayakumar 2013], due to the complexity and the importance of the pharmaceutical supply chain, anything less than a service level of 100% is unacceptable, since this has a direct impact on public health. For this reason, one acceptable solution which can be adopted by a pharmaceutical supply chain is to carry a huge amount of inventory in order to ensure a fill rate close to 100% , however, if a pharmaceutical company adopts this level of inventory, this increases the total costs assumed by the organization; it also represents a challenge since most of the medicines and products are perishable. It has been estimated that in supermarkets and medicines stores the cost of expiration is over 500 million dollars per year [Karaesmen 2011]. In addition to the perishability of medicines, pharmaceutical supply chains deal with the problems of demand uncertainty, limitations of space, legal regulations and patient safety.

2.2 Previous reviews related to pharmaceutical supply chain management

[Laínez 2012] describe real mathematical applications which have immediate or potential relevance to the pharmaceutical industry. The article is divided into the three key phases in the lifecycle of an innovative drug product: product development, capacity planning and supply chain management.

A study of the different areas of pharmaceutical supply chain management was completed by [Kwon I Kim 2016]. This considers strategic areas in which the supply chain must achieve efficiency in terms of costs, such as supplier relationship management, logistics operational tools and process improvement.

Another review has been carried out by [Narayana 2012] involving research on management issues in the pharmaceutical industry, and this study uses a classification in terms of geographical zones, research methodologies and managerial issues. The study is not dedicated to finding quantitative models in the pharmaceutical supply chains except for the identification of emerging issues for healthcare practitioners.

A further study [Privett 2014] identifies the 10 main global health supply chain challenges. The challenges are found to be lack of coordination; inventory management; absent demand information; human resource dependency; order management; shortage avoidance; expiration; warehouse management; temperature control; and shipment visibility. Another point of view is presented by [Alverson 2003] in which the main challenges faced by pharmacies are divided into a lack of inventory control; excess inventory levels; frequent stock outages and costly emergency deliveries; increased health system labor requirements; workflow interruptions and expensive

work; and missed contract compliance.

[Shah 2004] draws on the literature to present the most important issues in supply chain design and operation: primary and secondary manufacturing, operational issues such us demand and inventory management and strategic and design issues.

A recent review of material logistics in hospitals is presented by [Volland J., Fugener A., Schoenfelder J., Brunner J. 2017]. In this review, the logistical activities of hospitals are studied and several opportunities for future research are identified and classified into supply and procurement, inventory management, distribution and scheduling and holistic supply chain management.

[Settanni 2017] develop a review of pharmaceutical supply chain from the point of view of operational research models. This review make emphasis in the design, formulation and solution of mathematical models in the pharmaceutical supply chain sector determining which type of reconfigurations can be done by implementing technology interventions in medicine manufacturing.

In conclusion, there are reviews that have developed different approaches to typify and characterize logistics problems in hospitals and medicines supply chains as material logistics in hospitals, supply chain design an operations in hospitals or challenges in global health supply chain. Nevertheless the review presented in this chapter is focused on the quantitative models in the pharmaceutical supply chain, a subject not studied in depth in the previous reviews on healthcare logistics. Additionally, in this chapter is presented a new taxonomy based on the actors of the pharmaceutical supply chain.

2.3 Publications selection process

2.3.1 Framework for literature classification

As the main objective of this review is focused on quantitative models on pharmaceutical supply chain, the triangle of logistic strategy proposed by [Ballou 1997] has been used as the framework for literature classification. Considering this triangle of logistic strategy, three major research topics within the literature for the quantitative models in the pharmaceutical supply chain are proposed: (1) design of the pharmaceutical supply chain network; (2) hospital inventories; and (3) optimization of pharmaceutical supply chain networks. The literature is thematically classified using this framework.

Category (1) comprises the activities involved in the design of a supply chain network in the pharmaceutical sector; this includes the selection of a manufacturer's points, and the capacity of production plants, warehouses and distribution points. Category (2) takes into account decisions related to the inventory of medicines in hospitals and pharmacies. Finally, in category (3), models related to the optimiza-

tion of a pharmaceutical supply chain are presented. The main difference between topics (1) and (2) is that the first topic is related to the strategic decisions, while the second topic is related to the operational decisions for a distribution network.

2.3.2 Identification of publications

In order to identify the relevant literature, different keywords were used to identify the principal articles. The keywords used for the first topic were "pharmaceutical supply chain network design", "pharmaceutical supply chain design" and "pharmaceutical multi-site planning". For the second topic, the keywords used were "hospital inventories", "inventory hospitals", "pharmaceutical inventories", "medicine inventories" and "optimization inventory hospitals": Finally, the keywords used for the third topic were "pharmaceutical supply chain optimization"; "optimization pharmaceutics" and "medicine optimization supply chain network".

The review was carried out using the following databases with English-language published papers: Informs Journals, Proquest, Sciencedirect, Springerlink, Taylor and Francis Group, Wiley Online Library, Emerald and IEEExplore. The search process included research articles published between 1984 and 2020.

The selection criteria of this review fall into two categories: First, papers that consider quantitative models for any echelon of the pharmaceutical supply chain presented in Figure 2.1 and second any type of paper or research focused on applications to pharmaceutical supply chain or the optimization of any stage of the logistics of medicines.

In this way the inclusion criteria have the following characteristics: (i) original research developed that met any field of the taxonomy proposed in this research, (ii) paper written in English presented before in the range between 1984 to 2020, (iii) research papers studying quantitative models and quantitative applications in the pharmaceutical supply chain, (iv) papers listed in one of the databases mentioned before. The exclusion criteria have the following characteristics: (i) it was not listed in the databases of quantitative methods or models or applications of quantitative models in healthcare or supply chain, (ii) qualitative studies in pharmaceutical supply chain management, (iii) case studies in pharmaceutical sector (iv) quantitative models in supply chain that does not include any echelon in the chain or does not belong to the taxonomy proposed.

2.4 Review

2.4.1 Supply chain network design

According to [Shah 2004] the design of a supply chain network consists of the selection of the optimal logistical configuration of a new pharmaceutical supply chain. Decisions related to the configuration of a supply chain networks involve the manufacturing stages, and can be divided into primary manufacturing for active ingredients and secondary manufacturing for formulations and packaging, storage facilities, secondary sites, warehouses, product market areas, distribution networks and vehicle routing optimization . Although there are a considerable number of studies of the development of models for the supply chain network design, only a small proportion of these works are related to the pharmaceutical sector.

One of the first studies of network design for the pharmaceutical industry was developed by [Rotstein ' 1999]. In this paper, the authors develop an optimization model for product development, introduction strategy, capacity strategy and investment strategy. In order to solve the problem, the authors use a two-stage stochastic programming method; the first stage includes the decisions that must be made immediately, while the second stage includes decisions about capacities. In the second stage, a large number of scenarios are used for the different combinations of outcomes of the independent clinical trials for different drugs. A similar approximation to this problem was developed by [Papageorgiou 2001]. In this paper, an optimization-based approach is developed for selecting product development, introduction strategy and capacity planning. The problem is formulated in terms of a mixed-integer linear programming model, taking into account the global trading structures and the particular features of manufacturing active pharmaceutical ingredients. Extensions of this work were presented by [Levis 2003] and [Levis 2004]. In the first approximation, the authors develop a multi-scenario mixed integer programming method and present a hierarchical algorithm for reduction of the computational time. In the second approximation, they propose a systematic mathematical programming approach for long-term multi-site capacity planning under conditions of uncertainty. The problem is formulated as a two-stage, multi-scenario, mixed-integer linear programming model and can determine both the product portfolio and the capacity planning. A hierarchical algorithm is proposed for reducing the computational time.

[Gatica 2003a] develop a model that considers a group of pharmaceutical plants which plan to manufacture a set of various products. Products are divided into two types: those for which demand can be considered deterministic, since they are already in the market and forecasting can be derived reasonably well, and those for which demand is stochastic. The authors develop a mathematical optimization model to determine the final product portfolio, capacity planning, optimal production planning and the sales and inventory planning profiles. Due to the large number of products and scenarios, this implementation is only useful in small in-

stances. In order to solve this problem, the same authors develop an aggregation approach [Gatica 2003b]. The results of the proposed approach show that a substantial improvement in computational time is achieved by using the aggregation scheme.

Another model focusing on the capacity planning for product introduction has been proposed [Chambers 2009]. The focus of the article is not only on demand uncertainty but also on technical uncertainty. Specifically, these authors evaluate the use of process flexibility in risky new product development in the pharmaceutical industry. The proposed model is solved using stochastic dynamic optimization in order to determine the optimal capacity and allocation decisions for a flexible facility.

A complete model for multi-site, multi-echelon, multi-period enterprise planning and global network of a pharmaceutical company is developed by [Susarla 2012]. The model integrates procurement, production planning and distribution with the effects of international tax differentials, inventory holding costs and other real-life factors. The proposed model is evaluated over two real sets of data although this does not include stochastic uncertainty.

For the case of the design of a pharmaceutical supply chain network under fuzzy uncertainty, [Mousazadeh 2015] develop a bi-objective mixed integer linear programming model in order to determine the opening of manufacturing and distribution centers and the flows over the logistic chain. The parameters involving uncertainty which are included in this model are demand, unit manufacturing costs, unit transportation and transshipment costs and safety stock levels. In order to test the proposed model, real data is used, collected from a national organization. Finally multi-objective decision-making techniques are used and tested on the data collected for the problem. It can be concluded that although this is a very important topic due to its impact on the community, applications in the pharmaceutical sector are focused only on the manufacturing process, despite the design and configuration of a new pharmaceutical supply chain network requiring specific elements that belong to this sector.

[Savadkoohi 2018] present a combination between location and inventory decisions considering the medicines as main product. In this work authors includes three different echelons of the pharmaceutical network manufacturers and distribution centers, and decisions of inventory are also made considering the perishability of medicines. Two different parameters are considered as a source of uncertainty, the demand and the production capacity. Given this, a possibilistic programming approach using fuzzy optimization is used and a real case study is analyzed.

[Zahiri 2018] propose an analytical model for the pharmaceutical network design considering products perishability, substitutability and quantity discount by using robust possibilistic programming approach. The objective function consists in a contrast between the minimization of the total costs and the minimization of the

maximum unmet demand. The uncertainty considered is related to demand and costs where a fuzzy approach is used.

[Halim 2019] propose a systematic framework for the design of sustainable pharmaceutical network by integrating computer tools within analytic hierarchy process. Finally, [Nasrollahi 2019] present an integrated pharmaceutical supply chain network design with maximum expected coverage. Different echelons have been considered such as distribution centers, hospitals and manufacturers and they have include the information of patients demand. In this article also a reliability index is proposed for improving the service level to patients. Authors proposed a multi-objective optimization model contrasting the total costs and service levels where a NSGA algorithm is used and the model is tested over a real case of Iran.

In the majority of these articles, the type of demand used is deterministic and is not used for a large variety of medicines. Since most of the articles use a deterministic approach, the trends used in the quantitative models are classical linear programing models and the development of heuristics. Future research in this topic may include the configuration of real pharmaceutical supply chains including uncertainty aspects of the configurations. A summary of publications related to the quantitative models in pharmaceutical supply chain network design and its classification based on sources of uncertainty, type of demand, number of medicines, supply chain components and methodology is presented in Table 2.1

Author	Source of Uncertainty	Type of Demand	Number of Medicines	Supply Chain Components	Methodology
Rotstein et al. (1999)	Consumption of manufacturing resources	Deterministic	8	Manufacture	Stochastic programming
Papageorgiou et al. (2001)		Deterministic	8	Manufacture	Optimization
Levis et al. (2003)		Deterministic	7	Manufacture	Optimization Heuristic
Levis et al. (2004)	Clinical trials outcomes	Deterministic	7	Manufacture	Optimization Heuristic
Gatica et al. (2003a)	Demand	Deterministic stochastic	12	Manufacture	Optimization
Gatica et al. (2003b)	Demand	Deterministic and stochastic	12	Manufacture	Heuristic
Chambers et al. (2009)	Demand and technical aspects	Stochastic	5	Manufacture	Stochastic dynamic optimization
Susarla et al. (2012)		Deterministic	8	Manufacture Warehouse Waste treatment plant	Optimization
Mousazadeh et al. (2015)	Demand Costs	Stochastic	1	Manufacture Distribution center	Multi-objective optimization
E. Savadkoohi et al.(2018)	Demand Capacities of production	Fuzzy	2	Manufacturer Distribution Centers	Fuzzy approximation-optimization
Zahiri et al. (2017)	Demand Costs	Fuzzy	15	Manufacturers (primary and secondary) Distribution Centers	Fuzzy optimization
Iskandar et al. (2019)		Deterministic	1	Manufacturers Suppliers Distribution centers	AHP-Optimization
Meisam et al. (2019)	Demand	Fuzzy	1	Distribution centers Factory Hospital	Genetic Algorithms

Table 2.1: Publications on quantitative models of supply chain network design

2.4.2 Pharmaceutical inventory problems

This section identifies problems related to inventory control in pharmacies and hospitals. Inventory models are one of the most studied problems in the literature, although inventory management in the pharmaceutical supply chain has been given little attention. [Almarsdóttir 2005] describe key factors that pharmaceuticals and hospitals must take into account for inventory control for medicines and other kinds of consumer products. Certain specific features are studied, for instance the perishability of products, lead times, and constraints on capacity among others.

A first approach to inventory management in a hospital was developed by [Åatir 1987]. This paper presents a stochastic and periodic review model in which the objectives used are formulated in terms of stock-out and budget. The model contemplates the use of three kinds of medicines, and results are analyzed with a sensitive analysis.

[James Little 2008] develop a constraint-based model for determining stock levels for all products at a storage location with space constraints, which takes into account the criticality of medicines. The decision variables are related to the service level, the frequency of delivery and the amount to order up. The objectives are the maximization of the minimum service level and the maximization of the average service level. The models are tested using 110 different medicines. This model is an extension of a previous article presented by [Vincent 1984].

One of the first extended models was proposed by [Dellaert 1996]. Their proposed model is an extension of the (R, s, S) model. It is denoted as the (R, s, c, S) model and is obtained using the EOQ model. The proposed model considers stochastic demand and is tested using a planning horizon of 100 time periods and 1544 items. After implementation in the hospital and an evaluation, it was determined that the total costs are reduced.

Another approximation of an inventory model has been developed by [Kelle 2012]. These authors formulated two exact models for decisions at an operational level. The first is an (s, S) model with space constraints; the parameters are assumed to be random variables and shortages are allowed. The second model is formulated in terms of optimal allocation based on ordering and holding costs, which are considered to be a service level constraint rather than a shortage. Through the use of this model it is demonstrated that the total cost of pharmaceutical inventory can be reduced by up to 80%.

An approximation of inventory control via simulation was developed by [Vila-Parrish 2008]. The model involves two stages; the first consists of the development of a Markov decision process to represent medicines' demand as a function of the patient condition, allowing the determination of the appropriate medicines' inventory levels. The second phase consists of the use of simulation to evaluate the

inventory policies characterized in the first phase. In this simulation model, the lead times and fixed production costs are not considered. In contrast to this approximation, [Dengfeng 2015] develop a simulation model using system dynamics . In this article, the demand is approximated as a normal distribution and a safety stock is used. The scenarios used in the simulation show that shortages can be reduced. Another approximation using system dynamics was developed by [Wang 2015]. Using the results of their simulation, these authors develop a dynamic drum-buffer-rope replenishment model. A Powell search algorithm is used to determine buffer sizes and inventory quantities. The model is tested on real data, demonstrating that the model can find the optimal replenishment timing and quantity, minimizing the total cost and with no stock-out occurrence.

[Çaklcl 2011] present an approximation to the pharmaceutical inventory models using RFID . In this article, the authors demonstrate that continuous review is superior to periodic review in terms of costs whenever accurate real-time information is available with no additional cost. The proposed model takes into account only one product, and the demand is modeled as a continuous stochastic process with stationary and independent increments. The lead time is assumed to be deterministic and a constant number and shortage are backordered. While this model does not consider the economic effect of the use of RFIDs, [Matthieu-P. Schapranow 2012] develop some approximations of the real costs of the use of RFIDs in the pharmaceutical supply chain. While most of the objective functions consider the minimization of total costs, [Gökçe 2016] consider the maximization of the total net profit. The problem is formulated by these authors as a mixed-integer linear programming model with a hybrid time representation. The model considers the use of the VMI (Vendor Managed Inventory) strategy with three months of planning horizon and 15 products.

[Guerrero 2013] propose a model for a multiproduct multi-echelon process . The demand is assumed to be stochastic, Poisson-distributed and independent between products. The problem is formulated as a Markov chain with the objective of minimizing the stock-on-hand value. The model determines both the re-order level and the order-up-to level. A heuristic algorithm is proposed to reduce the computational time.

A mathematical model using two forms of stochastic data has been developed by [Rappold 2011]. This is the only article that assumes a stochastic bill of materials for the procedures in an operating room; in addition, a stochastic demand is assumed. The authors develop a mathematical model using stochastic uncertainty and test this using real data.

Two exact models for lost sales and limited storage capacity have been developed by [Bijvank 2012]. In the capacity model, the service level is maximized subject to a capacity constraint; in the service model, the capacity required is minimized subject to a service level constraint. Moreover, the authors develop an heuristic for the capacity model in which the re-order levels and order quantities are fixed.

[Maestre 2018] present an application of Model Predictive Control to a real case of inventory management in a hospital of Spain where 10 different medicines are tested to evaluate the performance of the model. Different constraints are used such as ordering quantities, stock levels and space constraints and the purpose is to minimize the total costs. Results of the proposed approach generates a reduction over the total costs.

[Ahmadi 2020] develop a stochastic multi-echelon (s,S) periodic inventory control model also considering the perishability of medicines. The problem is formulated as stochastic mixed integer linear programming model where two different purchasing strategies are analyzed: if the depot orders fresh products and those with shortest product life. A genetic algorithm is developed for solving the proposed model.

It is important to mention that the majority of the articles deals with instances with a reduce number of medicines, despite the fact that in real cases, hospitals, clinics and pharmacies work with an extremely large number of medicines.

A summary of publications related to inventory problems in pharmacies and hospitals and its classification based on sources of uncertainty, type of demand, number of medicines, constraints, methodology used and objective function is presented in table 2.2.

Author	Source of Uncertainty	Type of Demand	Number of Medicines	Constraints	Methodology	Objective
Satir and Cengiz. (1987)	Demand	Stochastic	3	Budgetary Shortage Lead times	Stochastic optimization	Stock-out
Vincent et al. (1984)	Demand	Stochastic	1	Space limitation Delivery Criticality	Optimization	Total costs
Dellaert et al. (1996)	Demand	Stochastic	1544		Optimization	Total costs
Kelle et al. (2012)	Demand	Stochastic	12	Space limitation Service level Shortage	Optimization	Total costs
Vila-Parrish et al. (2008)	Demand	Stochastic	3	Shelf life	Markov Decision Process Simulation	Total costs
Dengfeng et al. (2015)	Demand	Stochastic	1	Space limitation	Simulation	Total costs
Wang et al. (2015)	Demand	Stochastic	1	Shortage Stock-out Space limitation	Simulation Heuristic	Total costs
Çaklcl et al. (2011)	Demand	Stochastic	1	Lead times Shortage	Stochastic optimization	Total costs
Gökçe et al. (2016)		Deterministic	15	Space limitation	Optimization	Total net profit
Guerrero et al. (2013)	Demand Trigger an order Delivery success	Stochastic	4	Space limitation Service level Quantity ordered	Markov Decision Process Heuristic	Total costs
Rappold et al. (2011)	Demand Bill of material	Stochastic	4	Space limitation	Optimization	Total costs
Bijvank et al. (2012)	Demand	Stochastic	1	Space limitation Service level	Heuristic	Service level Capacity
Little et al. (2008)	Demand	Stochastic	110	Space limitation Delivery Criticality	Optimization	Minimum service level Average service level
Maestre et al. (2018)	Demand	Stochastic	10	Placing orders Stock levels Storage Satisfaction of demand	Control Theory	Minimize costs
Masel et al. (2019)	Demand	Stochastic	1	Capacity Expiration quantities Inventory balance	Genetic Algorithms	Minimize costs

Table 2.2: Publications on quantitative models of pharmaceutical inventories

2.4.3 Optimization of the pharmaceutical supply chain network

An online procurement system has been developed by [Kim 2005]. In this model, a supply chain network is considered, involving a group of pharmaceutical companies, wholesalers and hospitals. Due to an online system implementation, real-time information is provided for optimizing the inventory control of pharmaceuticals. Through the use of the proposed model, the total costs can be reduced and a vendor management system strategy can be adopted which involves sharing information with wholesalers. [Baboli 2011] propose two models for centralized and decentralized supply chains. The basic model consists of one warehouse and one retailer, and the products are assumed to have a deterministic demand which corresponds to items with a stable demand and high turnover rate. The centralized model is considered to be a single organization in which the warehouse and the retailer belong to the same organization, while in the decentralized model the warehouse and the retailer are treated as external companies. Other works deal with the problem of optimization of a supply chain in a centralized model, such as that proposed by [Azzi 2013]; in this study, a system dynamic simulation model is developed using a careful analysis which demonstrates that logistics outsourcing is often the most economical choice. Nevertheless, the proposed model is only applicable to small instances due to the complexity of the interactions within the chain. While this model is a mathematical approximation, [Hassan 2006] have put forward an analysis based on the best practices for supply chain management; these authors generate eight possible scenarios and use a multi-criteria decision-making model to evaluate these.

[Uthayakumar 2013] develop a model that integrates continuous review with production and distribution. The model considers a set of products, variable lead times, payment delays, constraints of space availability and customer service level. The proposed mathematical model takes into account a random demand, a deterministic expiration date, and a random lead time that is assumed to be a normal random variable; the production rate of the medicines is also considered. The model is formulated as a two-echelon supply chain in order to identify the optimal inventory lot size by minimizing the integrated expected total cost. A Lagrangian relaxation is used to solve the proposed model. The same authors develop a model which involves a fuzzy stochastic environment [Priyan 2014]. The total cost of inventory management is considered as a fuzzy variable in a multi-echelon, multi-product, multi-constraint inventory based on the distance method. Another model that considers stochastic uncertainty has been proposed by [Zhao 2012]. The demand is assumed to be stochastic; information available for the model includes a set of prices from the manufacturers, the production rate and the initial inventory. The model is divided into the optimal policy for the manufacturer and that for the distributor, and proves that the solutions enhance the profits in the echelons of the chain. Finally, a heuristic to estimate the Pareto-improving fee range is proposed.

Although in the majority of the articles the authors describe a distribution network and its optimization, [Lawrence 2004] propose a model to evaluate the outsourcing of non-critical inventory items . The proposed model includes a comparison of a three-echelon distribution network versus an outsourced two-echelon distribution network. The model proposed for the three-echelon distribution network is an extension of the work of [Sinha 1991] and [Rogers 1991]. The proposed model takes into account only a single product, which has a stochastic demand. Two heuristics are proposed for testing the proposed model.

Although in most of the articles the authors develops models considering uncertainty, [Balcázar-Camacho 2016] and [Giuseppe 2016] develop a linear programming model for a distribution network. The model proposed considers a multi-echelon distribution system in which the objective function involves the minimization of the total costs. Although the mathematical models proposed by these authors consider some elements concerning the real composition of networks, the instances used for testing the model are small and do not correspond to the size of a real life supply chain network.

A real case of a pharmaceutical chain in India is studied by [Dutta 2007]. The authors describe a multi-period-based decision support system for planning within the pharmaceutical process. The model includes manufacturers and warehouses, decisions on materials and production activities. A mathematical linear model is proposed using seven types of medicines.

[Jetly 2012] propose a multi-agent simulation model for the pharmaceutical supply chain . The model is used to prove that the norms of a specific industry can be used to represent a specific industry capable of tracking its evolution. The model is tested with three kinds of medicines and includes 30 manufacturers, 60 suppliers and 60 distributors. The lifecycle is also modeled.

A different type of study was performed by [Eberlea 2014]. This study consisted of implementing a Monte Carlo simulation to reduce the lead times of the production processes. The main medicines involved in the simulation model are both parenteral and injectable medicines. The results of the simulation are evaluated with a "what if" technique to assess the effect of investments in resource allocation and process improvements.

[Masoumi 2012] propose a network oligopoly model. This model uses arc multipliers for supply chains using inequality theory. The model takes into account the perishability of pharmaceuticals and the objective is to maximize the product flows.

[Nyhuus Hansen 2015] consider the problem of supporting planning operations before market launch in the pharmaceutical supply chain. A two-stage stochastic

model to support the market launch preparation is developed in this study.

An algorithm for integrating decisions on inventory and purchases has been developed by [Rego 2013]. The model estimates the number, size and composition of purchasing groups for a set of hospitals with the objective of minimizing the supply chain costs. The proposed algorithm is based on the variable neighborhood search within a tabu metaheuristic search. The proposed algorithm is tested with two items and a set of 15 providers.

A coordination problem between plants in pharmaceutical supply networks is studied by [Grunow 2003]. These authors propose several aggregation schemes and a novel mixed-integer linear programming model formulation based on a continuous representation of time. A heuristic approach is developed in order to solve real-life problem instances.

An enormous number of studies on reverse logistics can be found in the literature; however, studies of reverse logistics within the pharmaceutical supply chain have not yet been highly developed by researchers. Reverse logistics in the pharmaceutical context consists of the collection of the unwanted or unused medications from pharmacies or hospitals. The objectives of reverse logistics are diverse, and include the minimization of fees and penalties paid to governments by industry, maximization of unwanted products collected, maximization of individual profit, minimization of collection costs, and minimization of waste, among others [Narayana 2014].

A real case of reverse flow within the pharmaceutical industry is developed by [Amaroa 2008]. At the planning level, an aggregation description is proposed for the supply chain operational model. A master representation is defined to support supply chain resources, and a mathematical formulation is then proposed for optimal supply chain planning. Once the results of the supply chain planning are obtained, the scheduling model is formulated using a mathematical model.

As described above, few works can be found on reverse logistics applied within the pharmaceutical sector. [Weraikat 2016] propose a linear programming model with a Lagrangian relaxation including a negotiation with 3PL (Third-Party Logistics) providers. [Shih 2003] have presented a multi-criteria optimization approach to minimize the total cost of collection system planning for medical waste; a similar work is presented by [Weraikat 2016] in which a nonlinear mathematical programming model is developed. [Xie 2012] designed a green pharmaceutical supply chain model to reduce pharmaceutical waste. Although other studies of reverse logistics include several other features, quantitative models are not included.

[Sabouhi 2018] propose an integrated approach based on Data Envelopment Analysis (DEA) combined with two-stage possibilistic stochastic programming integrating the supplier selection and quantity discount for procurement and raw materials. Models are tested over a real life instance where also resilience analysis are performed.

[Moslemi 2017] propose a multi-objective optimization model considering production rates and quality and green concepts. This model uses three different objective functions, the minimization of the manufacturing costs, the maximization of the quality level of production and the minimization of the environmental effects of transportation. Given that is a combinatorial optimization problem, it is solved by using a Non-Sorting Genetic Algorithm (NSGAII) algorithm. Different sizes of instances are tested for analyzing the performance of the algorithm.

[Lin 2019] study the problem of medical supply from the point of view of processing and distributing. The proposed mathematical model considers the efficiency in each one of the levels established including constraints of demand satisfaction, capacities of warehousing and manpower. Finally an algorithm is developed and tested over real case instances.

Most of the articles in this part of the review include uncertainty in demand, which is modeled as a stochastic function. Nevertheless, real approximations of pharmaceutical problems in hospital are not deeply developed in the literature. Future research on this topic should include coordination between various medicines and should develop powerful algorithms to handle the very large number of items.

A summary of publications related with optimization of the pharmaceutical supply chain network and its classification based on sources of uncertainty, type of demand, number of medicines, constraints used, objectives, methodology used and supply chain components is presented in table 2.3.

Author	Source of Uncertainty	Type of Demand	Number of Medicines	Constraints	Objective	Methodology	Supply Chain Components
Kim (2005)		Deterministic			Total costs	Optimization	Pharmaceutics Wholesalers Hospitals
Baboli et al. (2011)		Deterministic	7	Vehicle capacity Warehouse capacity	Total costs	Optimization	Warehouse Retailer
Azzi et al. (2013)		Deterministic	3	Warehouse capacity	Total costs	Optimization Simulation	Warehouse Hospitals
Hassan et al. (2006)		Deterministic	8	Warehouse capacity	Total costs	Multi-criteria decision making	Warehouse Hospitals
Uthayakumar et al. (2013)	Lead times Demand	Stochastic	3	Lead times Payment delays Perishability Production rate	Total costs	Lagrangian relaxation	Warehouse Pharmacy
Priyan et al. (2014)	Total cost Lead times Demand	Stochastic	3	Lead times Payment delays Perishability Production rate	Total costs	Optimization	Warehouse Pharmacy
Zhao et al. (2012)	Prices Demand	Stochastic	1	Production rate Budget	Profit	Heuristic	Manufacturer Distributor
Lawrence et al. (2004)	Demand	Stochastic	1	Backorder Service level Warehouse capacity	Total costs	Heuristic	Manufacturer Warehouse Pharmacy
Sinha et al. (1991)	Demand	Stochastic	1		Total costs	Optimization	Warehouse Pharmacy
Rogers et al. (1991)	Demand	Stochastic	1	Budget	Total costs	Lagrangian relaxation	Warehouse Pharmacy
Balcázar-Camacho et al. (2016)		Deterministic	3	Production rate Warehouse capacity	Total costs	Optimization	Manufacturer Warehouse Pharmacy
Giuseppe et al. (2016)		Deterministic	4	Production rate Warehouse capacity	Total costs	Optimization	Manufacturer Warehouse Pharmacy
Dutta et al. (2007)		Deterministic	7	Production rate Warehouse capacity	Total costs	Optimization	Manufacturer Warehouse
Jetly et al. (2012)	Demand	Stochastic	3	Life cycle	Total costs	Simulation	Manufacturer Supplier Distributor
Eberlea et al. (2014)	Demand	Stochastic	2	Lead times	Total costs	Simulation	Manufacturer Warehouse
Masoumi et al. (2012)	Prices Demand	Stochastic	1	Perishability	Product flows	Inequality theory	Pharmaceutics
Nyhuus et al. (2015)	Demand Authorization	Stochastic	1	Production rate	Total costs	Stochastic optimization	Manufacturer
Rego et al. (2013)		Deterministic	2	Warehouse capacity	Total costs	Metaheuristic	Supplier Pharmacies
Grunow et al. (2003)		Deterministic	5	Lead times Production rate	Total costs	Optimization Heuristic	Manufacturer
Amaroa et al (2008)		Deterministic		Warehouse capacity Vehicle capacity	Total costs	Optimization	Supplier Pharmacies
Weraikat et al. (2016)		Deterministic		Warehouse capacity Vehicle capacity	Total costs	Optimization Lagrangian relaxation	Supplier Pharmacies
Shih et al. (2003)		Deterministic		Warehouse capacity Vehicle capacity	Total costs	Multi-criteria optimization	Supplier Pharmacies
Weraikat et al. (2016)		Deterministic		Warehouse capacity Vehicle capacity	Total costs	Optimization	Supplier Pharmacies
Xie et al. (2012)		Deterministic		Warehouse capacity Vehicle capacity	Waste	Optimization	Supplier Pharmacies
Fatemeh et al. (2018)	Capacities	Deterministic	12, 15 and 20	Pre-positioned inventory Capacity Flow balance Discount level	Minimization of the total costs	Fuzzy-DEA, chance-constrained programming	Suppliers manufacturers
Mahmood et al. (2017)	Capacities	Deterministic	1	Capacity Flow balance Inspection Satisfaction of demand	Minimization of the total costs	Stochastic Optimization	Suppliers manufacturers
Shiva et al. (2017)		Deterministic	3	Environmental effects Capacities Selection of technology	Minimization of the manufacturing costs Maximization of the qualitity level production Miniization of the environmental effects	NSGA-II	Plants Suppliers Hospitals Collection centers
Huidan et al. (2019)		Deterministic	1	Satisfaction of demand Capacities Distribution Manpower	Maximize efficiency	Decomposition	Hospital Distribution centers

Table 2.3: Publications on quantitative models of optimization of the pharmaceutical supply chain

A conclusion can be drawn that most of the articles regarding optimization of the supply chain models take into account only a small number of medicines, thus reducing the complexity of the interactions between the echelons and the medicines.

2.5 Contribution of the thesis in relation to the literature

In this chapter a literature review of quantitative models of the pharmaceutical supply chain is presented based on three classification categories. The taxonomy proposed shows that 23% of the publications corresponds to network design, 27% corresponds to inventory problems and 50% corresponds to supply chain optimization models.

Several deterministic models are found, but the majority of publications use a stochastic approach of modeling uncertainty in some of the echelon of the chain. Most of the articles involve stochastic modeling, and only a few uses an alternative approximation of uncertainty, for example fuzzy logic and robust optimization, among others. In network design 66% of the articles the demand is considered as deterministic and 16% as stochastic and 16% of the articles used both types of demand. Inventory models 93% of the articles the demand is considered as stochastic and 7% as deterministic. In supply chain optimization 64% of the articles the demand is considered as deterministic and 36% as stochastic.

Related to the techniques found in this literature review, for network design the most common technique used is classic optimization with 33% of the cases, while combination between classic optimization and heuristics was used in 17% of the cases and stochastic optimization, heuristics, stochastic dynamic optimization and multi-objective optimization was used each one of them with 8% of the cases, finally fuzzy optimization is used in 17% of the cases. On inventory models the most common technique used is classic optimization with 47% of the cases while stochastic optimization is used in 13% of the cases, Markov decision process with simulation, simulation, simulation with heuristic, Markov decision process with heuristic, heuristics and control theory are used with 7% each one. In supply chain optimization the most common technique used is classic optimization with 41% of the cases, heuristics with 10% of the cases, simulation, lagrangian relaxation s with 7%, stochastic optimization, metaheuristics and multi-criteria optimization are used with 7% of the cases respectively and also inequality theory, lagrangian relaxation with optimization and multi-criteria decision making are used 3% of the cases respectively.Finally, judging from the number of publications in this area, pharmaceutical supply chain is a significant topic with important real-world applications; however, despite some recent developments, there remain few works on this subject.

Given this review, the main contributions of this thesis related to the literature can be summarized as follows:

From the point of view of optimization of pharmaceutical systems, this review shows that only one article includes several sources of uncertainty that affects the decision making of managing medicines in hospitals (see [Priyan 2014]). For this reason in chapter 4 an application of simulation-optimization approach based on the stochastic counterpart or sample path method is used for optimizing tactical and operative decisions in the pharmaceutical supply chain in hospitals taking into account multiple sources of uncertainty associated with the information in different echelons of the chain such as patients (medicines demand) and distributors (medicine costs and lead times). Based on this approach, two mixed integer programming (MIP) models which correspond to the stochastic counterpart approximating problems were formulated. These models support the decision making of replenishment of medicines by considering real characteristics of the system (expiration dates, emergency purchases the service level required, perishability, aged-based inventory levels and emergency purchases, multiple suppliers) and combining different sources of uncertainty.

On the other hand, from the point of view of optimization of pharmaceutical systems, this review shows that the concept of multi-source resilience strategy in the pharmaceutical supply chain has not been addressed. In chapter 5 two mathematical models are developed to optimize the process related to unit-doses and prescriptions management and distribution in a network of hospitals where also a location-allocation of pharmacy robots decisions are evaluated. One of these models consider the uncertainty of the demand of medicine by using the p-robustness approach and consider the concept of resilience to avoid the risk of centralized distribution processes in a very sensitive network managing the demand of medicines and prescriptions. This chapter contributes to the healthcare location-allocation literature by addressing a real application in the context of automation of unit-doses and prescription preparations, including the uncertainty in demand of medicines and resilience.

Even when the studies of quantitative models combine different kinds of techniques, this review shows that there is a lack of the use of combined techniques that will allow researchers to approximate the operation of a pharmaceutical supply chain in a realistic way. For this reason in chapter 3 is proposed a conceptual modeling framework using causal loop diagrams to characterize the dynamics of the pharmaceutical supply chain and its impact in the hospital medicines management. Based on this conceptual framework, a system dynamics simulation model was built to have a first approximation of the cost of managing medicines in hospitals, including the legal regulation. In the same sense there are some illnesses that must be treated as special due to its complexity of treatments and the high costs that represents to the health system, for this reason, in chapter 6 machine learning models are used

to predict the pharmaceutical expenditure in a specific case of a chronic disease (diabetes).

Finally, this review shows that in the most of the mathematical models found in the literature treats the demand as a source of uncertainty. In this way is recognized that the correct estimation or modelization of the demand is a key factor for optimizing the systems. For this reason in chapter 7 machine learning models are used for predicting medicines demand in seasonal epidemics, that is considered a high variability periods where the consumption of some medicines increases.

Chapter 3

Characterization of pharmaceutical supply chain and simulation of medicines' costs in hospitals

Contents

This chapter presents a conceptual modeling framework using a causal loop diagrams to characterize the dynamics of pharmaceutical supply chain and its impact in the hospital medicines management. Based on this conceptual framework a system dynamics simulation model was built by using the main variables that affect the medicines managing costs in hospitals including the legal regulation related to reimbursement values, service level and unit-doses preparation. A real case of a hospital in Colombia was studied to explore how the dynamics of the variables selected affect the behavior of the final unit-dose cost of medicines. The model were validated by using real data.

3.1 Introduction

In recent years, the medical cost per capita for medical outpatients and inpatients has increased due to variables that are not easily manipulated by decision makers,

such as the increase of life expectancy, the growing population, and the emergence of new diseases, among others. According to official statistics from the World Bank, the global population is growing at a rate of 200,000 per day, and it is higher in countries with medium and low incomes [wb2 2015a]. Another factor that increases the demand for health services is the substantial increase in life expectancy; currently, according to the World Health Organization (WHO), the life expectancy is 73 years for a woman and 68 years for a man [wb2 2015b].

The healthcare system is composed of different actors as shown in Figure 3.1. The main actors are patients who require health services. The biological environment generates the pathologies that increase the demand for services and treatments. On the other hand, the government creates policies for medical services, where public and private entities such as pharmacies and hospitals are responsible for managing the healthcare service, all framed within an economic environment. There are also the producers that can be divided into: research and development, generic manufacturers, local manufacturers, contract manufacturers and biotechnology companies [Shah 2004].

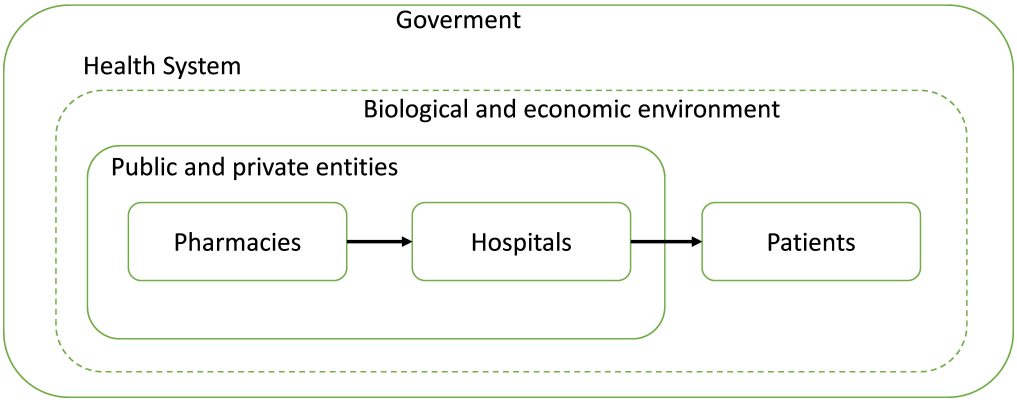

Figure 3.1: Healthcare system [V. Mantzana, M. Themistocleou 2007]

The pharmaceuticals industry, like many other industries, is a complex system [Shah 2004], principally due to the processes, operations and organizations involved in the discovery, development and manufacture of medicines.

Pharmacies, clinics and hospitals operate in a very regulated market. Governments and regulatory entities fix the prices for producers, distributors and hospitals, imposing the margins for each of the players in the supply chain [Shah 2004]. While producers can establish their own times for producing and distribution, wholesalers and pharmacies must guarantee a service level according to the demand. The economic crisis and monetary limitations are forcing pharmacies to change the way

they made decisions related to purchasing, ordering more frequently and in lower volumes, so the warehouses must work with these requirements in order to synchronize the supply chain [Shah 2004]. Besides the regulations and the economic crisis, the pharmaceutical supply chain is affected by medicines' perishability and shortages [Nagurney 2013].

The system studied in this chapter consists of a market heavily regulated by governmental policies. Medicines given to patients by hospitals are paid by the government but a maximum refund value that hospitals can access has been established. So, it is possible for hospitals to gain or lose money in the process of buying medicines from companies or providers, and the whole process is related to the administration to patients. With this specific system, it is interesting to answer the following questions: What is the behavior of the final cost of medicines? What actors are involved in the process and how is their interaction with the system studied? What is the variation of the real cost of administering medicines to patients?

As the system studied is complex and involves several actors, the main purpose of this chapter is to provide an approximation to understand the pharmaceutical system dynamics and its impact in the hospital medicine management and its costs to identify losses or gains. The models can be used as a framework to determine the maximum prices that the regulation agencies can pay to hospitals (reimbursements) considering the real issues that affects the final prices.

3.2 Background

Different approaches are used to determine the cost of medicines from the medicine manufacturers to the administration to patients. Some models provide a statistical function to estimate the price of a brand-name medicine and a generic substitute [Ferrara 2012]. The model considers the quantity of firms that produce the medicine and constructs a utility function of a representative consumer with market and product segmentation by using a sensitivity analysis in which the boundaries of medicine consumption with ranges of prices are obtained.

[Kaiser 2014] propose a pricing regression model to infer the change of prices due to a legal reform in Denmark, where medicine prices are regulated by a set of reference prices. The regulation of prices has been used in other countries and it has been evaluated in the literature [Brekke 2011],[Brekke 2007],[Brekke 2009],[Miraldo 2009]. A similar work was developed by [Lauenroth 2017] and [Mohamed 2016], who studied pharmaceutical pricing in Germany and in Egypt respectively. The model evaluates the effect of changing the medicine prices. With this change, they show that consumers tend to

substitute branded medicines.

In [Haji 2009] a fuzzy logic model to estimate the medicine pricing for a new medicine using fuzzy logic is developed. Fuzzy logic is used for the representation and acquisition of knowledge and data uncertainty. This model uses the product life cycle to estimate different factors that affect the medicine pricing during different stages of the life cycle.

In [Li 2014] is developed a model to study the behavior of pharmaceutical costs in China using system dynamics. The model addresses problems related with the high prices of medicines and pharmaceutical fees and takes into account a problem related to the unnecessary use of expensive medicines by medical staff. The model is based on articles that deals the hospital's problems with system dynamics [Rauner 2002], [Chaerul 2008], [Hassmiller Lich 2010], [Rwashana 2009], [Sirois 2008]. [Kunc 2013] developed a system dynamics simulation model to represent the pharmaceuticals market for chronic cardiac disease in Bulgaria. The main idea of the simulation model is to test different policies related with medicine regulation, like providing timely access to the market, influencing the prescribing of generic medicines and implementing programs for increasing the percentage of diagnosed patients, based on the dynamics of the pharmaceuticals market for one chronic disease.

In [Abdollahiasl 2014] a system dynamics simulation model is developed. In the study authors propose a simulation model studying 92 different variables that are associated with the medicine policies in India. Authors first identify the different variables associated and create a causal loop diagram and then a Forrester model is proposed.

3.3 Methods

The pharmaceuticals supply chain process is a complex and dynamic system with multiple non-linear relationships. For this reason, this study uses a simulation continuous-time modeling approach [Forrester 1961]. System dynamics was selected to develop this study because its ability to evaluate different strategic policies and integrate the system feedback and delays, as well as to evaluate the relationship between the main variables and their impact on the behavior of the final price of medicines. The main objective is twofold: (i) build a conceptual causal-loop diagram that represent the entire process of the general process of managing medicines and (ii) generate a simulation model that enable to study the behavior of the final costs of medicines within hospitals. The main limitation of this work is related with the lack of information which implies that some variables cannot be modeled.

3.3.1 Causal loop diagrams foundations and dynamic hypothesis

System dynamics modeling requires the development of a causal loop diagram which captures the interactions between the key components [Asish Ghosh 2015]. Based on the factors involved in the pharmaceuticals process of the hospital, causal loop diagrams are developed.

The causal-loop diagrams were built based on the fieldwork carried out in the hospital and based in some studies which have identified some variables that affect the costs of medicines. For example [Brekke 2011] develop an econometric study to analyze the competition between different pharmaceutical companies and how this competition affects the selling price of medicines. In the same way [Kunc 2013] develop a system dynamics simulation model to study the effect of competition in the chronic cardiac disease market, finding that allowing competition in this type of market could generate savings in the final cost of medicines and hence on the public health system. [Kaiser 2014] study how governmental regulations of reference pricing systems can influence the final prices of medicines. [Abdollahiasl 2014] identified 93 different variables related to the final cost of medicines to analyze different governmental policies, some of these variables are the consumption, pharmacy inventory levels, competitions of distributors, among others.

The hospital selected for this study is divided into operational areas. The areas analyzed in this study are: (i) the pharmaceuticals area and (ii) logistics and supply chain area. The main objective of the pharmaceuticals area is to provide the hospital with the medicines required for patients. The pharmacy oversees receiving medicines, making records in the databases and updating inventory records for medicines, packaging medicines as individual items (a legal requirement to guarantee a medicine's traceability), keeping the inventory in good order, receiving the requirements from the clinic and dispatching in the right quantities and conditions. The pharmacy sends the requirements for medicines to the logistics area. The logistics area negotiates with suppliers to get discounts on the amount of medicines needed. Once a patient is healthy, the hospital makes a request to the local government to receive payment for the medical treatment. In Colombia, there is a regulation that establishes the range of prices for some medicines and treatments, so hospitals are not able to receive payments over the maximum legal price allowed.

The system dynamics model was developed in order to capture the behavior of the final cost of medicines within hospitals, describing the interaction between the main variables and parameters involved. The main idea is to map the variation of the costs to contrast its value with the maximum reimbursement value defined by governmental agencies in order to define if the final cost of medicines can exceed or not the maximum amount of money that the hospital will be receive by the process of reimbursement. For this reason understanding the impact of the pharmaceutical supply chain in the hospital is the first step to develop the simulation model. In this way, a conceptual structure was developed and divided into three main sectors:

manufacturers-distributors, demand of medicines and pharmacy.

Manufacturers and distributors causal loop diagram

Figure 3.2 shows the causal loop diagram of manufacturers and distributors of medicines. The variables used are:

- Manufacturers and distributors: refer to the number of companies selling medicines to pharmacies
- Competition among manufacturers and distributors: refers to the pricing strategy for selling to pharmacies
- Medicines production: refers to the quantity of medicines produced and distributed by the manufacturers and distributors
- Medicine inventory on market: refers to the quantity available for selling to pharmacies
- Medicine price to pharmacy: refers to the selling price of medicines to hospitals and/or pharmacies

A market with manufacturers and distributors with competition is driven by a balancing feedback loop (B1). Higher number of medicine companies (manufacturers and distributors), imply the increasing of competition for getting a portion of the market, because companies are interested in reaching a major proportion of the market, meaning that there is major competition between manufacturers and distributors. Hence, as the competition increase, it generates a reduction of the selling price to hospitals and pharmacies. On the other hand, as the selling price of medicines increase, the market becomes attractive and the number of manufacturers and distributors will increase. When increasing production on the market a reinforcement process is presented (R1). Higher competition generates an increasing production of medicines, thus the market will have a high number of medicines on the market that generates more competition between manufacturers and distributors.

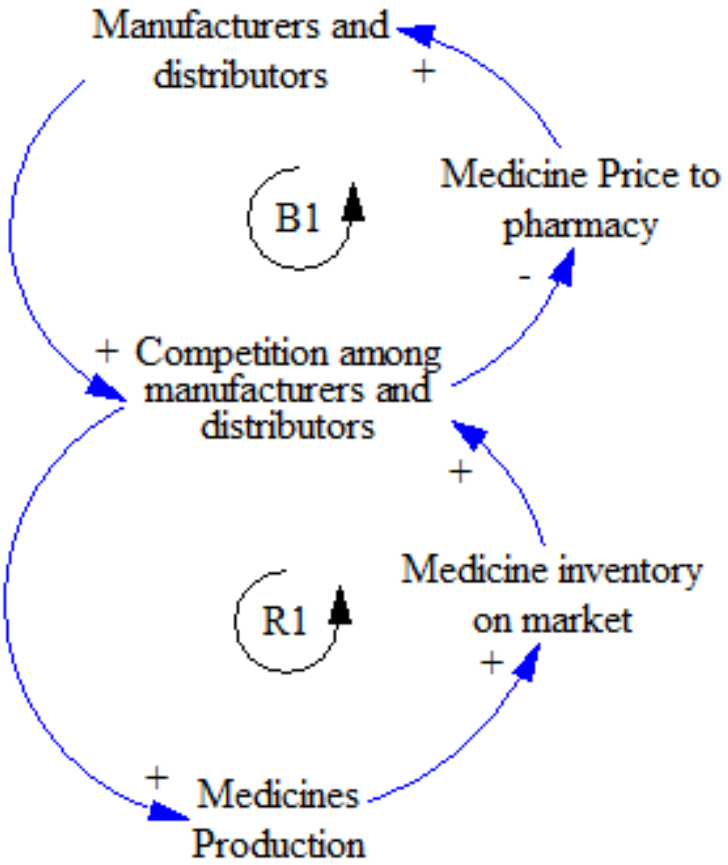

Figure 3.2: Manufacturers and distributors causal loop diagram

Demand of medicines causal loop diagram

Figure 3.3 shows the causal loop diagram of the demand of medicines, this causal loop is based on the very known illness causal loop developed in [Wittenborn 2016]. The variables used are:

- Infected population: refers to the quantity of population infected in a period
- Healing rate: refers to the rate that population is healing
- Medicines demand: refers to the consumption of medicines in hospitals
- Epidemiological environment: refers to the quantity of diseases and illnesses

A balancing feedback process (B2) is driven in the demand of medicines. The infected population is influenced by the epidemiological environment, the increasing

of infected population increases the medicines demand and the increasing of demand increases the healing rate. Finally, an increasing of the healing rate generates a reduction of the infected population.

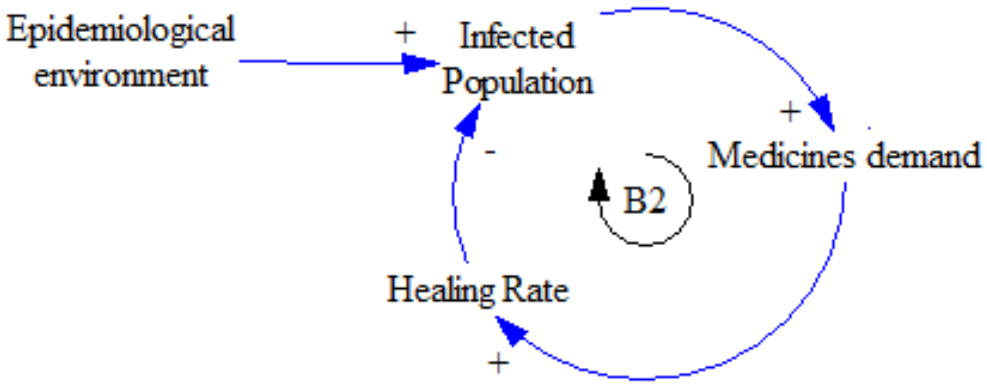

Figure 3.3: Demand for medicines causal loop diagram

Pharmacy causal loop diagram

Figure 3.4 shows the causal loop diagram of pharmacies. The variables used are:

- Pharmacy inventory: refers to the quantity of medicines available in the pharmacy
- Emergency purchase: in the case there are not enough medicines on the inventory and the patient needs the medicine at a specific time (used to guarantee the Colombian resolution 1604 2015 that indicates that hospitals must have a service level of 100%)
- Logistics costs: indicates the cost incurred by the staff at the pharmacy and hospital
- Adjustment costs: indicates the cost incurred with the adjustments of medicines (i.e cutting and packaging medicines into pills), the packaging of medicines into pills is mandatory for all hospitals by the Colombian resolution 1403/2007
- Governmental policies: indicates the legal regulation and policies of managing medicines in hospitals such us pills traceability, medicines managing and administration, among others

- Shortage: refers to the quantity of medicines that cannot be satisfied with the stock hold by pharmacies or hospitals
- Medicine unitary cost: refers to the final unitary cost of medicines

Internal processes and the definition of the final cost of medicines are dominated by three balance cycles (B3, B4 and B5). Higher level of inventory on pharmacy produce higher logistics costs driven by a balance cycle (B5), if the logistics costs increases, the medicine unitary cost also increases, but if the unitary cost increase the pharmacy inventory is reduced due to budget constraints. On the other hand, higher inventory levels produce less shortages with a balancing cycle (B4), and the increase of shortages produces an increasing in the emergency purchases, but if the inventory levels increases the emergency purchases decreases, also the increase of emergency purchases increases the inventory levels (B3) Higher inventory levels and emergency purchases generates higher adjustment costs. This adjustment costs are also influenced positively by governmental policies such as regulation of pills traceability and registration in public data bases. For this, an increasing in the adjustment costs generates an increase in the logistics costs. Finally, higher number of emergency purchases produces higher medicine unitary costs.

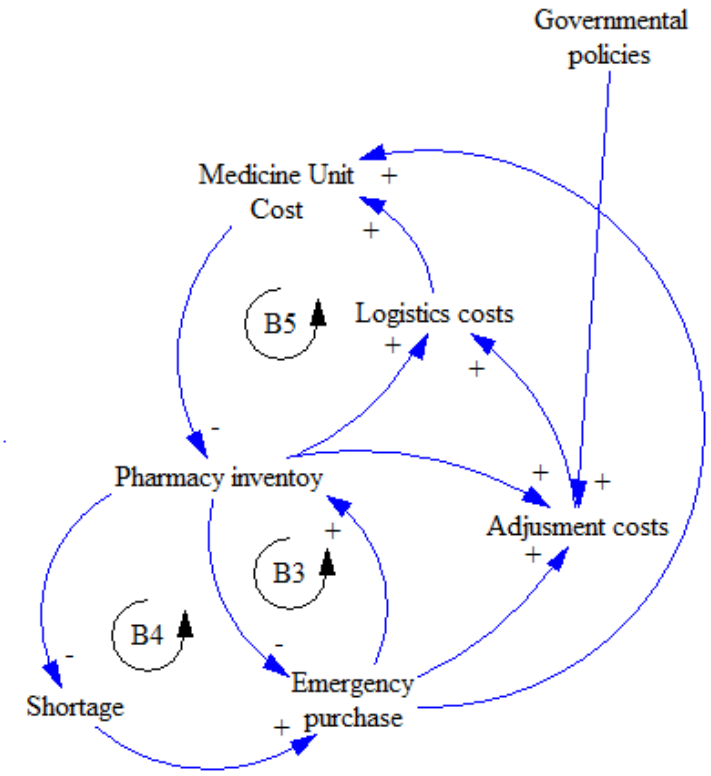

Figure 3.4: Pharmacy causal loop diagram

Causal loop diagram for the pharmaceutical supply chain

Figure 3.5 shows the integration of the specific causal loop diagrams shown in Figures 3.2, 3.3 and 3.4 , it represents the relationships in the pharmaceutical supply chain. Higher selling price from manufacturers produce less inventory levels, also this increment generates higher unitary cost of medicines, but this selling price is regulated or reduced by governmental policies. Finally, higher demand of medicines generates major shortages and reduce the inventory levels.

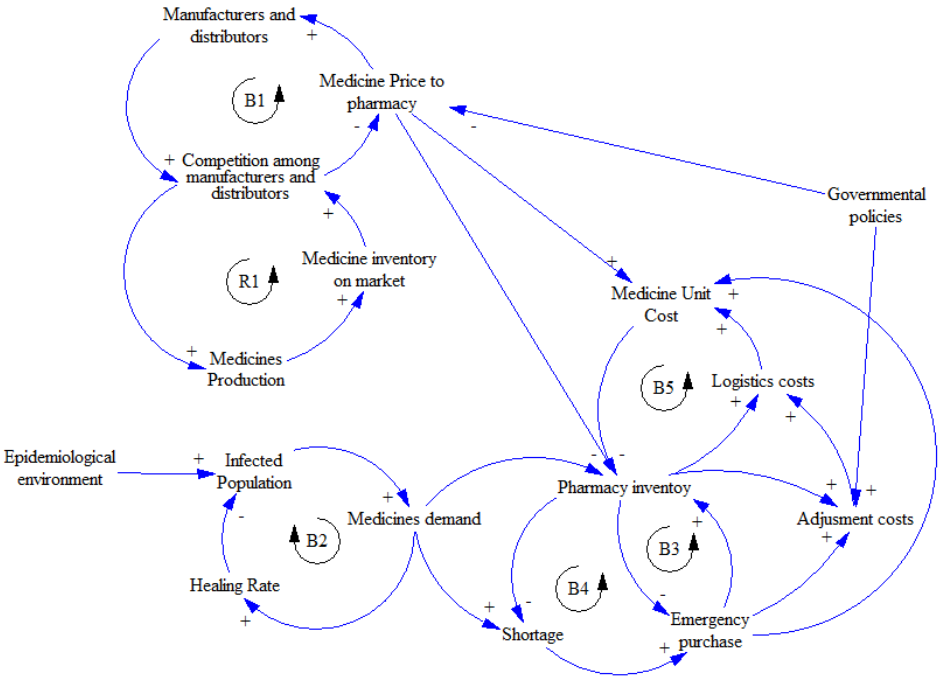

Figure 3.5: Causal loop diagram for pharmaceuticals supply chain

3.3.2 Data sources

Data were obtained from the administrative health databases of the hospital and from public databases. The model requires five categories of data: consumption of medicines, selling prices from manufacturers and sellers, lot size of medicines and legal regulation of prices.

Consumption of medicines: each patient arrives at the clinic and requires a specific medicine or set of medicines. The data used for the model is the total amount of consumption of each type of medicine in each month. Consumptions were obtained from the databases for a period of three years. Daily consumption was aggregated into monthly, to obtain the total amount of medicines that must be available in a single period. For each type of medicine and its consumption, a

goodness of fit test was developed.

Legal regulation of prices: The healthcare system is regulated by local regulation policies. Hospitals can define the final price of a medicine given to a patient, but this cannot exceed the maximum price defined by legal regulation. This is public available information.

Lot size of medicines: Each manufacturer and distributor have its own lot size of medicines. This information is given to the hospital.

Selling prices: Each manufacturer and distributor has its own selling price, and this is given to the hospital during each period of time.

3.3.3 System dynamics simulation model

The system dynamics simulation model was developed using Vensim V6.2. The delta time (DT) was defined as monthly during an interval of a year (12 months). Hospital manages more than 3000 references of medicines. For this study five (5) items of medicines that share the same space in the storage area was selected based on their high demand and differences in their range of prices, they can be provided by two different suppliers, who can deliver the product in 1 to 2 months. Demand can be supplied from the inventory or by an emergency purchase. In the case of an emergency purchase the pharmacy must find the medicine in the market, no matter what the selling price is, because the service level must be always 100%.

Table 3.1 shows the medicines selected for this study,their distributions and their statistical metrics were obtained based on the data given by the hospital. The first column presents the name of the medicine and the next shows the demand probability function (D Type) as result of a goodness of fit test performed for each medicine with p-values >0.15 based on 30 observations. As the demand for all medicines follows a normal distribution, the mean (in units) and the standard deviation (SD) are presented. In the fifth column, the selling price of medicines per unit is presented (PS) in $ COP is presented followed by the price increment if an emergency purchase is made (EI). (%L) is the percentage of medicine lost, this depends on factors like human mistakes or expiration dates. Inventory policy defined by the pharmacy in terms of re-order point (R) and order quantity (OQ) are presented, and the last column shows the lot size (LZ) which are standard over the different suppliers.

Medicine	D. Type	Mean	SD	PS	EI	%L	R	OQ	LZ
ACETAMINOFEN	Normal	4430.00	551.00	150	6-12%	Max 1%	5336	392	8
ACETYL	Normal	254.30	53.00	133	6-12%	Max 1%	341	62	13
ADRENALINE	Normal	182.95	95.60	1282	6-12%	Max 1%	339	55	4
AMLODIPINE	Normal	377.00	99.20	290	6-12%	Max 1%	540	33	20
AMOXICILLIN	Normal	27.40	29.60	1589	6-12%	Max 1%	76	7	12

Table 3.1: Medicine statistics

Following the methodology of system dynamics modeling, it is necessary to classify the variables into auxiliary variables, stock variables or flow variables. The simulation model comprises 15 stocks, 25 outflow rates and 35 auxiliary variables. Some other auxiliary variables, stocks and outflow rates have been included to facilitate the calculations and the output analysis. The description of the variables in terms of type, equations and units are presented in Table 3.2.

Name	Description	Type	Equation	Units
Demand P1	Parameter that generates the demand	Auxiliary Variable	INTEGER(RANDOM NORMAL(3591 , 5954, 4430, 551 , 1000))	Units of medicine 1
Emergency P1	Acummulation of emergency purchases	Stock	Flow Emergency P1	Units of medicine 1
Flow Ememrgency P1	Present the flows of emergency purchases	Flow	MAX(0, Demand P1-P1)	Units of medicine 1
Dec P1	Units of medicine use to satisfy the demand	Flow	MIN(Demand P1, P1)	Units of medicine 1
P1	Units on inventory of medicine 1	Stock	Inc P1-Dec P1-Lost P1	Units of medicine 1
Lost P1	Units of medicine on inventory lost	Stock	INTEGER(P1*MIN(RANDOM 0 1() , 0.01))	Units of medicine 1
Inc P1	Flow of units of medicine 1	Flow	Purchase P1*Size P1	Units of medicine 1
Size P1	Number of units of medicine 1 per package	Constant	8	Units per package
Total cost P1	Acummulation of the total costs	Stock	Inc Cost P1	Monetary ($)
Inc Cost P1	Calculation of the costs incurred	FLow	Price P1*(1+Emergency Price P1)*Flow Emergency P1+Purchase P1*Price P1+210*Size P1+0.03*P1	Monetary ($)
Price P1	Price per package of medicine	Constant	150	Monetary ($)/package
Emergency Price P1	Increment of the regular price when a emergency purchase is done	Auxiliary Variable	(RANDOM UNIFORM(8, 12 , 2))/100	%
Purchase P1	Units of medicine purchased using the R, Q policy	Auxiliary Variable	IF THEN ELSE(P1<=5336, 393 , 0) , RANDOM UNIFORM(1, 2 , 1) , IF THEN ELSE(P1<=5336, 393 , 0) , 0	Units of medicine 1
Fixed cost	Fixed cost due to logistics area	Constant	3000	Monetary ($)/order
Set up cost	Set up cost due to internal and governmental policies	Constant	210	Monetary ($)/unit of medicine
Unitary Cost P1	Unitary cost per medicine	Auxiliary Variable	IF THEN ELSE(Flow Emergency P1+ Purchase P1>0, (Flow Emergency P1*Price P1*(1+Emergency Price P1)+Purchase P1*Price P1)/(Flow Emergency P1+Purchase P1)+Set up cost+Fixed cost/(Flow Emergency P1)+Fixed cost/(Purchase P1), 0)	Monetary ($)/unit of medicine

Table 3.2: Description of variables used in the simulation model

The Forrester diagram for medicine 1 is presented in figure 3.6. The demand rate is obtained based on the information presented before; using this and the re-order point, the purchases that increase the flows of incoming medicines considering the lot sizing of each of them are obtained. Once a purchase is made, the quantity of medicines are accumulated increasing the levels of the variables (stocks or level variables). Medicines are accumulated, and the inflow rates (reduction of the levels of medicines) are the quantity of expired medicines and the demand. If there is

not enough medicine available, a flow of emergency purchases is used to satisfy the demand. Therefore, some auxiliary variables, flows and stocks (or levels) are used to obtain the total unitary cost.

The stocks are used to accumulate the amount of medicine 1 on inventory that can be used to satisfy the demand, this levels can be reduced also by the amount of product lost of the same type of medicine and the demand. The inventory increases by the total amount of purchases of medicine 1. Also, a stock for emergency prices and the cumulative cost of medicine 1 are used. Finally, an auxiliary variable of the unitary cost for each month is used to calculate all the expenses for the medicine.

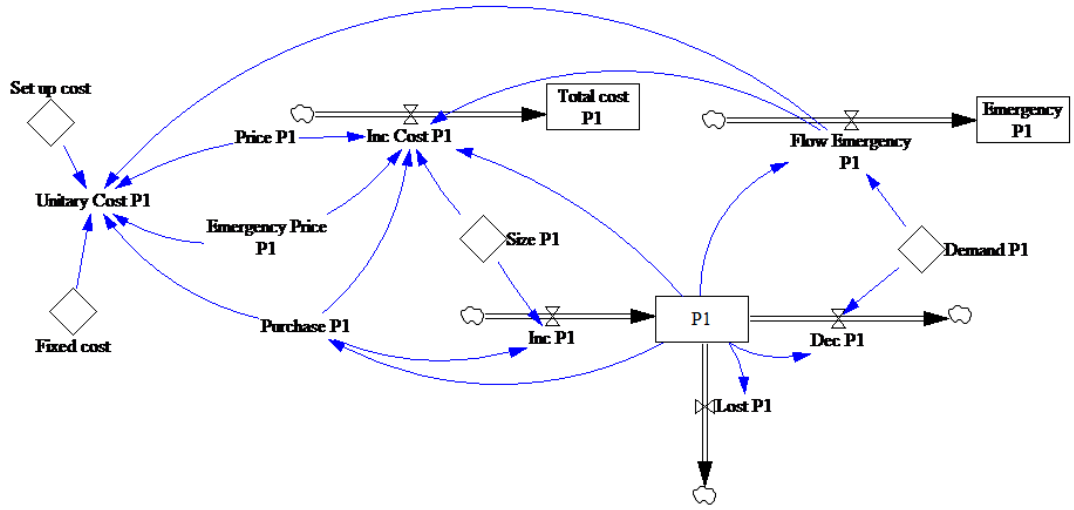

Figure 3.6: Forrester diagram for medicine 1

3.3.4 Validation

Structural model: Causal loop diagrams were built based on previous works in the field (econometric studies and system dynamics approaches in the pharmaceutical sector) see section 3.3.1 and the fieldwork developed in the hospital. The pharmacy area validated the elements of the diagrams and their relationships.

Simulation model: Based on the results of the simulation output a t-student test was used in order to validate the simulation model . Hypothesis testing techniques are used to determine if the average results of the simulation model are statistically similar to the real data for each type of medicine (final costs considering the uncertainty). For each medicine a confidence level of 95% was used and the results are provided in Table 3.3 based on 50 replications. Based on this it's possible to validate the results of the model.

Medicine	H0 Result	P-Value
ACETAMINOFENE	Not rejected	0.52
ACETYL SALICYLIC	Not rejected	0.13
ADRENALINE	Not rejected	0.23
AMLODIPINE	Not rejected	0.07
AMOXICILLIN	Not rejected	0.32

Table 3.3: Results of validation

3.4 Results and discussion

Figures 3.7, 3.8, 3.9, 3.10 and 3.11 show the effect of the administration of medicines in the final unit-dose costs (final costs in Colombian pesos in the y-axis).

Figure 3.7: Box plot final unit-dose cost medicine 1

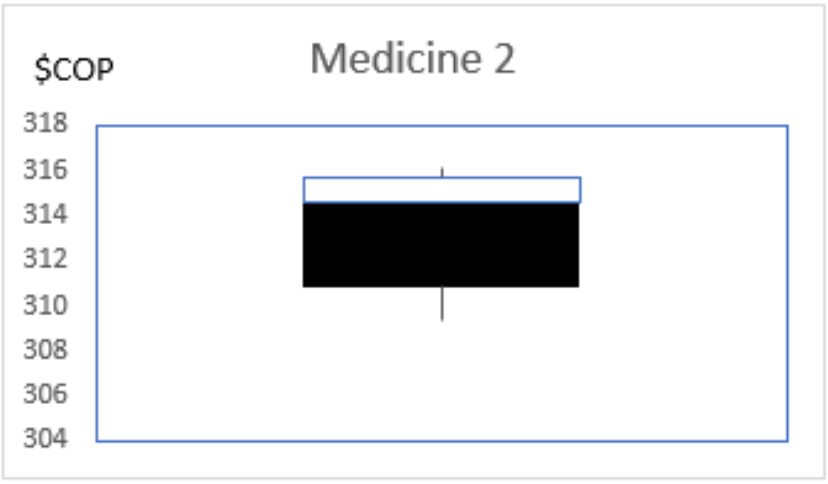

Figure 3.8: Box plot final unit-dose cost medicine 2

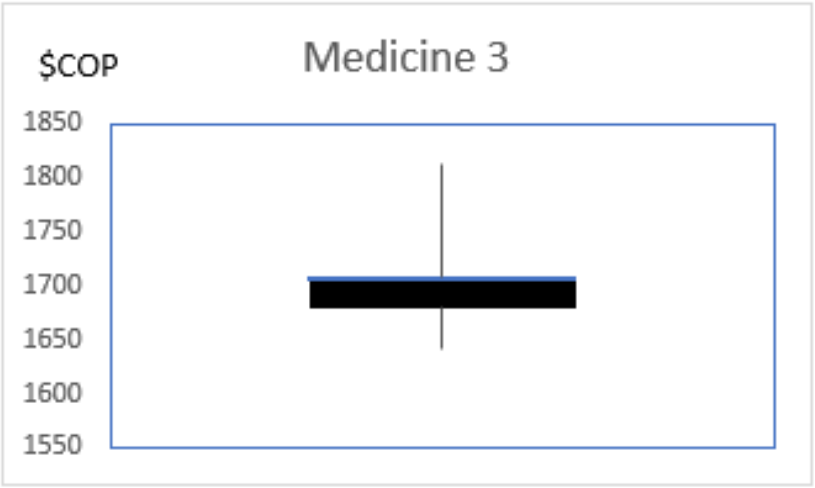

Figure 3.9: Box plot final unit-dose cost medicine 3

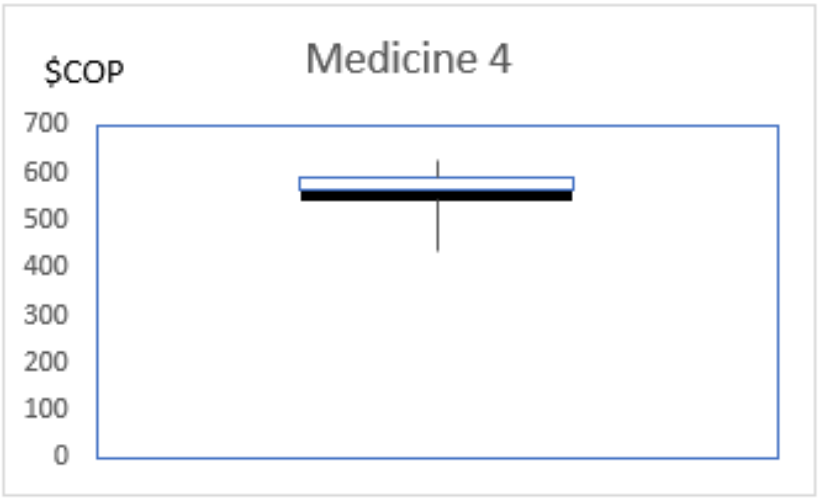

Figure 3.10: Box plot final unit-dose cost medicine 4

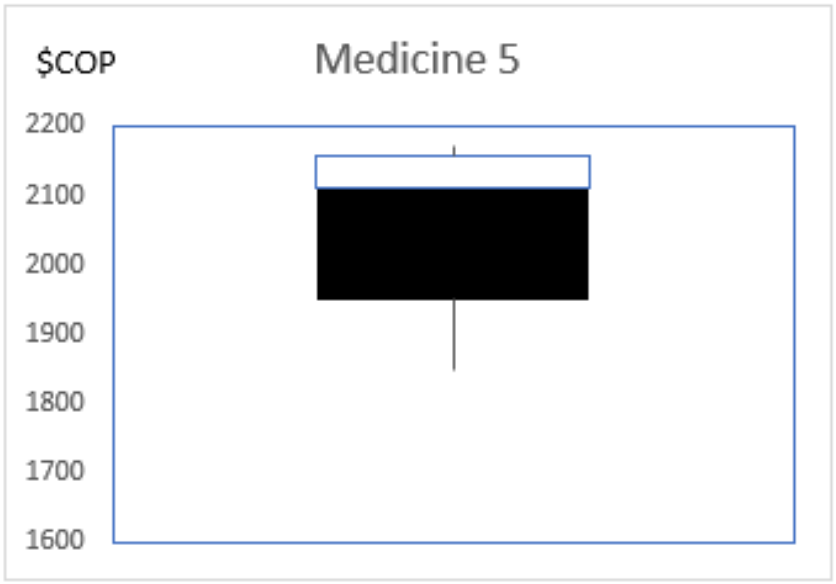

Figure 3.11: Box plot final unit-dose cost medicine 5

For medicines 1, 2 and 5 there is a high variation of costs, by contrast with medicines 3 and 4. This is explained by the supplying conditions of the hospital that includes a cost for cutting and packaging unit-doses. For these five medicines the final cost is increased by 158%, 137%, 41%, 116% and 36% respectively because of the interaction of all uncertainty sources and variables. Each of the medicines has its own behavior and they are affected in different ways by the complexity of

the system.

The effect of lead times and the re-order time (r,Q) policy over the planning horizon, coupled with the influence of other factors, creates irregular cost behavior, and their final costs change over time due to different influences. This result can help the hospital to determine the likely expenses and income for a financial planning horizon, but this model cannot determine the final cost of a medical treatment, which is out of the scope of this study.

It can be observed that for medicines with lower costs like medicines 1, 2 and 4 the final costs are duplicated, meaning that the logistics costs and other external factors have a high impact on the original price of the medicine. This means that the legal regulation about the reimbursement values of medicines may be ignoring these issues in the established policies.

These unit-dose cost variations are highly influenced by external factors such as market prices and expiration dates. Some detailed results for medicine 5 are presented in Figures 3.12, 3.13 and 3.14. Figure 3.12 presents the behavior of the unitary cost during the year (x-axis represents time and y-axis final costs), Figure 3.13 contains the behavior of the inventory levels (x-axis represents time and y-axis inventory levels), and Figure 3.14 presents the emergency purchases in the same period (x-axis represents time and y-axis emergency purchases).

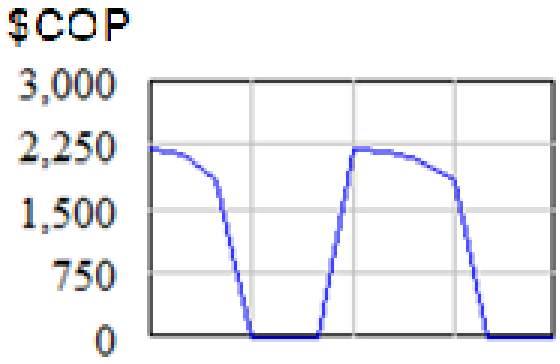

Figure 3.12: Behavior of unitary cost medicine 5

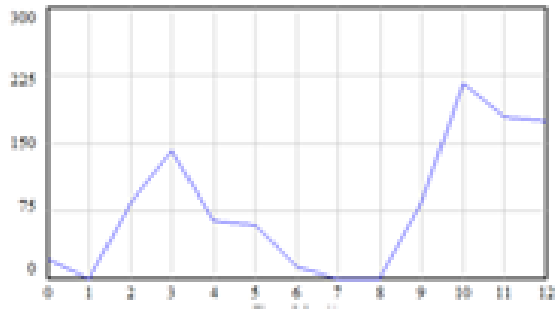

Figure 3.13: Behavior of inventory levels medicine 5

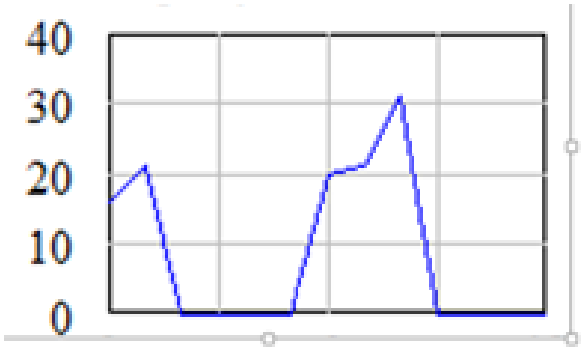

Figure 3.14: Behavior of emergency purchases medicine 5

It can be observed that the final costs of medicines do not have a linear behavior. Due to the lead times of manufacturers, sometimes there will be no medicine in the inventory (stock=0), a situation that triggers the purchase of emergency medicine, which increments the cost of the purchase. Also, it can be observed that the final costs do not always have the same influences. For example, in some periods 44% of the final cost is influenced by the stock and 56% is influenced by emergency purchasing, while in some other periods the final price is influenced by purchasing and emergency purchasing in different proportions. Also, in some periods of time the unitary cost is 0, a situation that occurs because in these periods there are no purchases or emergency purchases. In that case, demand is satisfied by the units remaining in the inventory.

Finally, Figures 3.15, 3.16 and 3.17 present the comparison between the range of the final unit-dose cost of a medicine and the reimbursement value (FOSYGA Law 1283 1996) for medicines 1 and 2, 3 and 5 and 4 respectively . (the point is the value of the current reimbursement approved by the government).

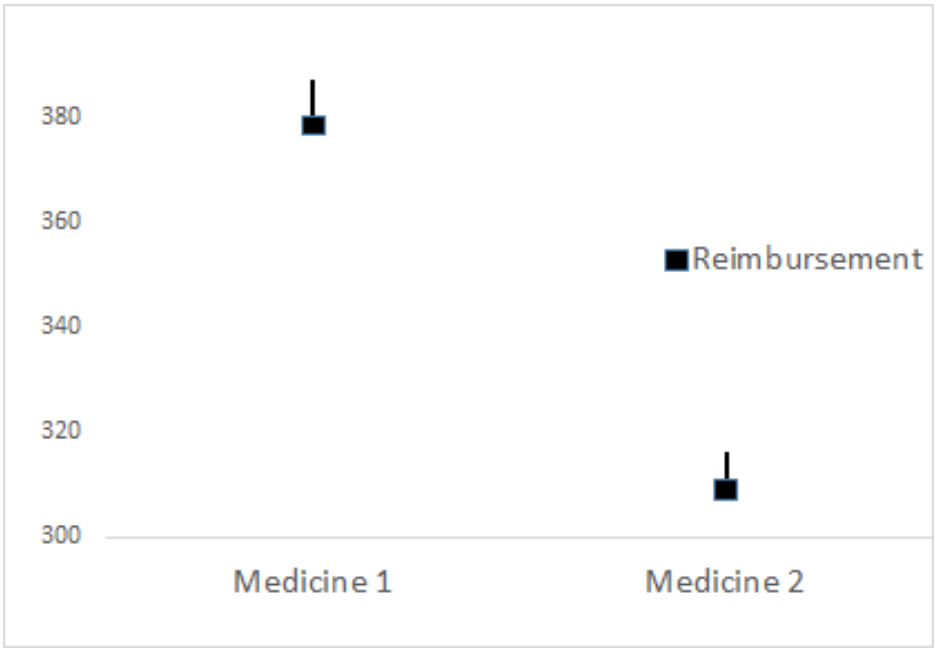

Figure 3.15: Reimbursement and range of costs medicine 1 and medicine 2

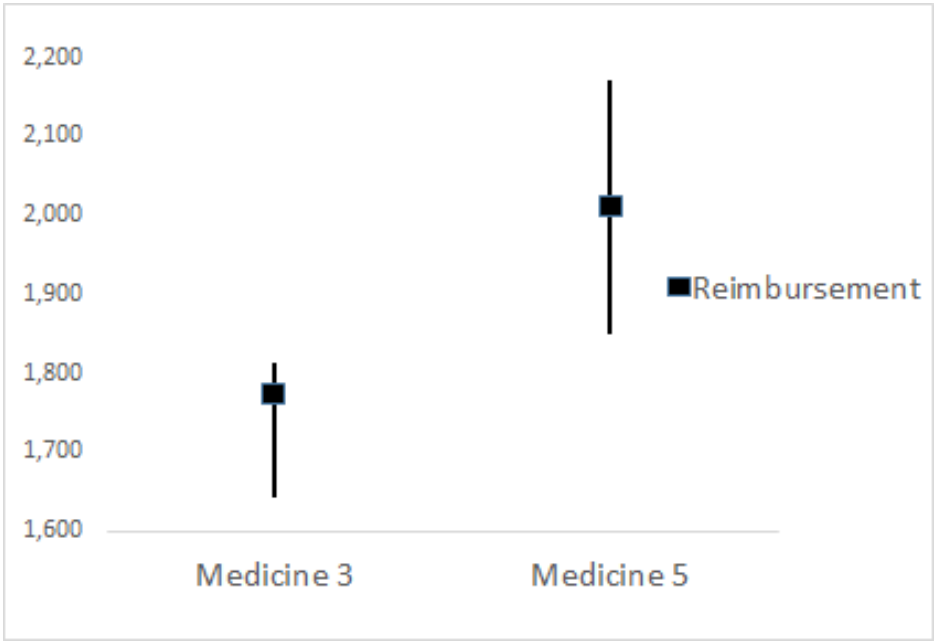

Figure 3.16: Reimbursement and range of costs medicine 3 and medicine 5

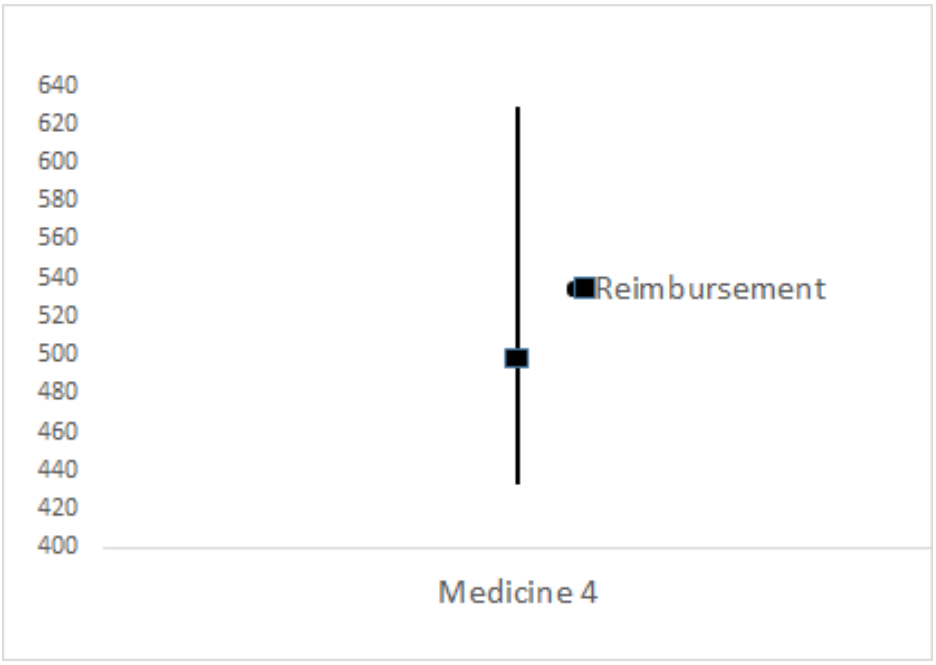

Figure 3.17: Reimbursement and range of costs medicine 4

In the cases of medicines 1 and 2, the value of reimbursement is less than the minimum value of the range. In the cases of medicines 3, 4 and 5, the value is between the extremal values. In the cases of medicines 1 and 2 there is no scenario in which the hospital can recover the money invested in medicines, or much less generate profits from the administration of medicines. This fact can be explained by the low unit cost of medicines, which makes the internal cost larger than its unit value and therefore does not reach the maximum value of the medicine.

On the other hand, it can be observed that the reimbursement values of medicines 3, 4 and 5 are within the range of variation of the price of the medicine, which means that there are possible scenarios in which the administration of medicines recovers the value of the medicines, in certain occasions generates some profits from their administration. However, this does not happen in all cases since there are external elements such as emergency purchases, medicine losses and variations in sales prices that directly affect the final cost of the medication, in addition to the hospital's internal administration.

3.5 Sensitive analysis

A sensitive analysis is developed to determine the variation of the final cost due to changes in some variables used in the model. In Figure 3.18 the sensitive analysis is presented based on the parameters shown in the Table 3.2. This analysis is

composed by four variations: (a) a variation of the set-up cost (costs related to orders management), (b) a variation of the fixed costs (cost related with pills traceability), (c) a variation of both parameters, set up cost and fixed cost and (d) a variation of the selling price. The range of variations for the first three cases are from 0 to the maximum value. In the case of the selling price the extreme case is considered in which the selling price of medicine is reduced to the half, this affirmation is not far from reality because there are some cases in which government establish or reduce the selling prices of medicines to hospitals. Analyzing the behavior between the changes of (a) and (b), it can observed that bigger variations are presented when changes are made with the set-up cost over the fixed cost. Also if both changes are made and the cost is reduced, the reduction over the final cost of the medicine can reach a 28%. Finally, over the graph (d) it can be concluded that the reduction over the final cost is mainly driven by the selling price of medicines, this can enhance to public and national governments to analyze and propose policies to control the selling prices.

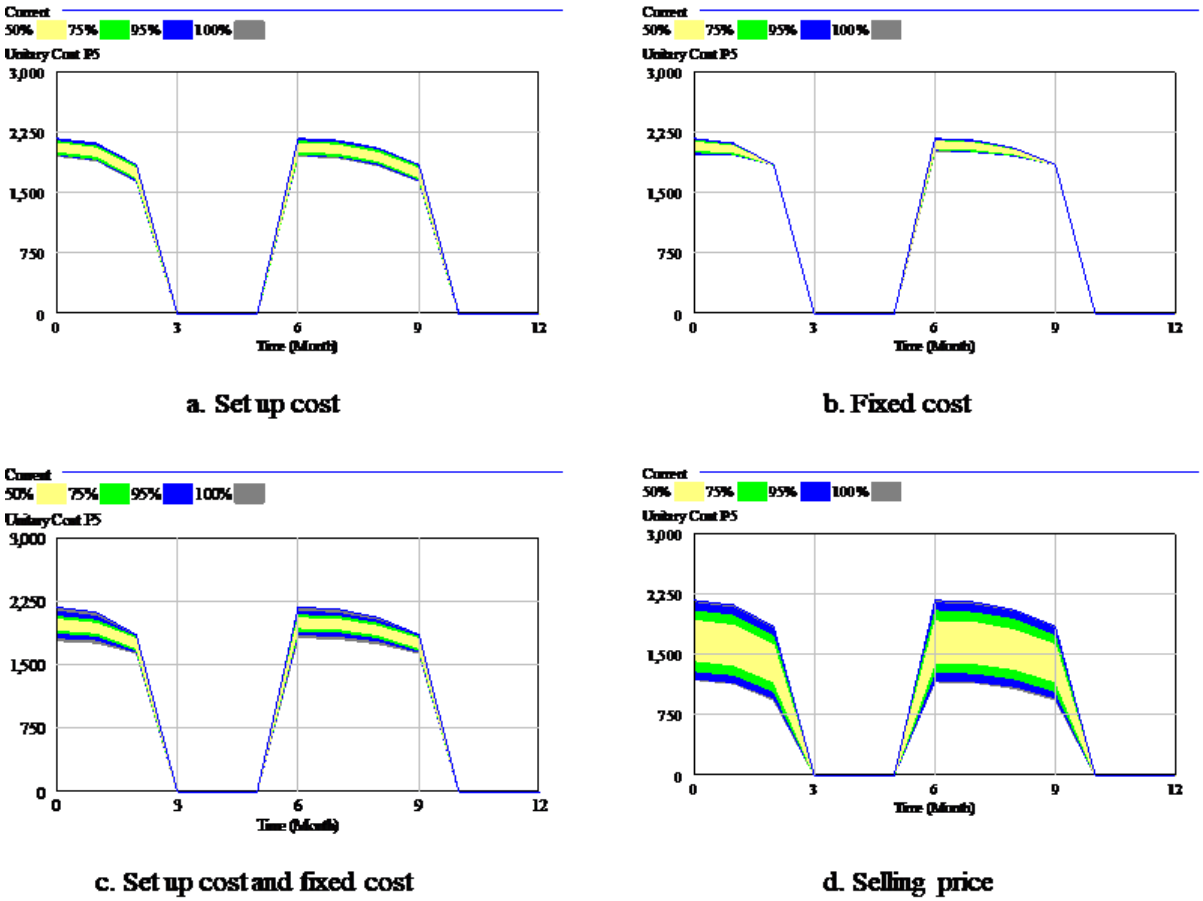

Figure 3.18: Sensitive analysis

3.6 Conclusions

This chapter presents a conceptual modeling framework using causal loop diagrams to characterize the dynamics of the pharmaceutical supply chain. Based on this, a system dynamics simulation model for the pharmaceuticals supply chain was developed in order to represent the impact on the final cost of medicines. The model was calibrated and tested based on currently available data in the hospital. From this study it can be observed that the final cost of medicines is not static and it is affected by different factors such as the amount of expired medicines, adjustment costs, logistic costs, emergency purchases and shortages. This model allows to understand the behavior of supplying medicines to patients and the behavior of the final cost of medicines, which is a key aspect due to the legal regulation of the reimbursement medicines in Colombia. The model developed can be used to explore different scenarios that will help decision makers to ensure alignment with the consumption of medicines by patients and to the final cost of medicines. The simulation model presented in this chapter is applied to a Colombian hospital, however it can be applied also in other pharmaceuticals systems. An analysis of the reimbursement values were presented, for this reason the approach in this chapter could be used as one of the elements to determine the maximum prices of medicines by legal regulation taking into account the particular conditions of the hospitals and the uncertainty associated.

Future research can include economic factors and policies used by pharmaceutical companies and pharmacies to fix the prices of medicines. Also, future work will include some optimization policies for the hospital to determine the best quantities of medicines and then try to reduce the unit-dose costs. Other future research will include the study of generic medicines, their effectiveness on patient health, and their impact in the total costs.

Chapter 4

Optimization under uncertainty of the pharmaceutical supply chain in hospitals

Contents

This chapter presents an application of simulation-optimization approach based on the stochastic counterpart or sample path for optimizing tactical and operational decisions in the pharmaceutical supply chain. This approach focuses on the pharmacy-hospital echelon, and it takes into account random elements related to demand, costs and the lead times of medicines. Based on this approach, two mixed integer programming (MIP) models are formulated, these models correspond to the stochastic counterpart approximating problems. The first model considers expiration dates, perishability and other elements related with legal regulations as the service level required, aged-based inventory levels, unit-doses preparation and emergency purchases. The optimal policy support decisions related to the replenishment, supplier selection and the inventory management of medicines. The results of this model have been evaluated over real data and simulated scenarios. The second model is a bi-objective optimization model solved with the epsilon-constraint method. This model determines the maximum acceptable expiration date, thereby minimizing the total amount of expired medicines.

4.1 Introduction

Supply chain management costs account for 25% to 30% of total costs in hospital expenses [Gebicki 2014]. Additionally, the costs associated with moving and handling medicines can vary between 35 to 40% of the total logistic costs [McKone-Sweet 2005]. The pharmaceutical industry is one of the most challenging industries in the world, since it is estimated that medicines consume about 10% to 30% (sometimes as high as 60%) of global health spending [Xu 2018]. Given the inherent differences between medicines and traditional industrial products, compared to the analysis of traditional supply chains, the analysis of pharmaceutical supply chains requires special considerations. For example, some medicines and surgical supplies must be available for use at all times [James Little 2008], and medicines have strict regulatory requirements related to the length of manufacturing time, distribution, product shelf life, and the reimbursement values that can be obtained by the government or the insurer [Almarsdóttir 2005]. In addition to these characteristics which make it different from other supply chains, the pharmaceutical supply chain deals with uncertainty; for example, the demand of each medicine is uncertain and can be influenced by seasonal changes. Moreover, due to the regulatory conditions, the costs and reimbursement values can be uncertain.

In some countries, health expenses can vary between 7 to 10% of the total gross domestic product and the pharmaceutical costs take up a large portion of this total, reaching approximately 10% [Priyan 2014]. Hospitals and clinics face several problems, such as the high and variable prices of medicines, physical and monetary constraints and the medicines' expiration due to their perishability. The managers of hospitals have given importance to this context in order to optimize pharmaceutical supply chain decisions, such as supplier selection, expiration dates, quantities, and supply system performance indicators. Models for determining optimal replenishment policies for single products can be found in the literature; however, these studies are not easily applied in hospitals since the range of medicines must be analyzed as a whole because they can share space or monetary resources. Moreover, the medicines' individual characteristics, such as obsolescence and internal costs, must also be considered. The inventory management of medicines presents two types of risks: demand can exceed supply, resulting in shortages; or, supply can exceed demand, resulting in surplus inventory [E. David Zepeda 2016]. Therefore, it is important to develop models and tools that integrate these specific elements and provide good criteria for the decision makers.

In this context, the goal of this chapter is to develop mathematical models to determine replenishment policy and expiration date selection of medicines considering different sources of uncertainty and other elements related with legal regulations by using a simulation-optimization approach in order to minimize the overall cost of managing medicines in hospitals.

4.2 Background

Different authors have studied the problem of medicine inventories and developed optimization models by considering different types of constraints and different types approaches to model the uncertainty of information as fuzzy, robust, probability functions, among others. Different reviews have been carried out by [Kwon I Kim 2016], [Narayana 2012], [Narayana 2014], [Franco 2017], [Volland J., Fugener A., Schoenfelder J., Brunner J. 2017], [Laínez 2012] and [Garcia 2015]. The most common constraint considered in the literature to model inventory problems is the space constraint. A first approximation to this model was proposed by [Vincent 1984]. They proposed an extension of the basic periodic review model by giving a cost to the space required keep an item. The space constraint is included in the objective function that minimize the total cost, this model considers a single medicine. [James Little 2008] developed a constraint-based model that considers the criticality of medicines and determines stock levels for all products at a storage location with space constraints. The decision variables are related to the service level, the frequency of delivery and the amount to order up. The objectives tested are the maximization of the minimum service level and the maximization of the average service level. The models were tested by using 110 different medicines. This model is an extension of the article presented by [Vincent 1984]. Other authors have developed approximations to problems with similar characteristics however these models are not developed in the context of medicines or hospital inventory management [Liang-Yuh Ouyang 2015], [Chou 2009], [Chung 2012], [Tsai 2013] and [Priyan 2015].

Other approximations for inventory management in hospitals have been developed by [Åatir 1987]. This paper presents a stochastic and periodic review model in which the objectives used are formulated in terms of stock-out and budget. The model contemplates the use of three kinds of medicines, and results are analyzed with a sensitivity analysis. [Guerrero 2013] proposed a Markov chain to model the problem using order up to level policies and considering stochastic demand, batching, emergency deliveries, and service levels. Also, a heuristic is proposed to find near-optimal replenishment solutions.

[Dellaert 1996] proposed an extension of the (R, s, S) model. It is denoted as the (R, s, c, S) model and they use the classic version of the EOQ model. The proposed model considers stochastic demand and it is tested using a planning horizon of 100 time periods and 1544 items. After implementation in a hospital and an evaluation, it was determined that the total costs were reduced.

Another approximation of an inventory model has been developed by [Kelle 2012]. Two exact models for decisions at the operational level were formulated. The first model is based on a (s, S) model with space constraints; some parameters are assumed to be stochastic where shortages are allowed. The second

model is formulated in terms of optimal allocation based on ordering and holding costs with service level constraints. Using this model, it is demonstrated that the total cost of pharmaceutical inventory can be reduced by up to 80%. In [Samira 2016] authors propose a stochastic inventory model with the main objective of mitigate the shortages in a healthcare facility.

An approximation of inventory control via simulation was developed by [Vila-Parrish 2008]. The model involves two stages; the first consists of the development of a Markov decision process to represent medicines' demand as a function of the patient condition, allowing the determination of the appropriate medicine inventory levels. The second phase consists of the use of simulation to evaluate the inventory policies characterized in the first phase. In this simulation model, the lead times and fixed production costs are not considered. In contrast to this approximation, Dengfeng et al. developed a simulation model using system dynamics [Dengfeng 2015]. In this paper, the demand is approximated as a normal distribution and a safety stock is used. The scenarios used in the simulation show that shortages can be reduced. Another approximation using system dynamics was developed by [Wang 2015]. Using the results of their simulation, these authors developed a dynamic drum-buffer-rope replenishment model. A Powell search algorithm was used to determine buffer sizes and inventory quantities. The model was tested on real data, demonstrating that the model can find the optimal replenishment timing and quantity while minimizing the total cost and avoiding stock-outs.

Pharmaceutical inventory models have been analyzed taking into account RFID (Radio Frequency Identification) technologies [Çaklcl 2011]. In this article, the authors demonstrate that continuous review is superior in terms of costs to periodic review whenever accurate real-time information is available with no additional cost. The proposed model considers only one product, and the demand is modeled as a continuous stochastic process with stationary and independent increments. The lead time is assumed to be deterministic and a constant number and shortages are backordered. While this model does not consider the economic effect of the use of RFIDs, [Matthieu-P. Schapranow 2012] develops some approximations of the real costs of the use of RFIDs in the pharmaceutical supply chain.

While most of the objective functions consider the minimization of total costs, [Gökçe 2016] consider the maximization of the total net profit. The problem is formulated as a mixed-integer linear programming model with a hybrid time representation. The model considers the use of the VMI (Vendor Managed Inventory) strategy, a planning horizon of three months and 15 products.

[Gebicki 2014] proposed a simulation method for testing different inventory policies by considering the medicines' characteristics such as such as provision through multiple dispatching machines, unit costs, availability of suppliers, criticality levels and expiration dates. For testing the policies, a simulation model was developed.

The policies tested were based on classic models, such as reorder point quantity models; the demand was assumed to be normal, and they used the lead times as a deterministic value defined by the suppliers. With the simulation model, they also tested which characteristics of medicines were important in choosing a policy, the authors conducted 2000 statistical tests to determine the importance of these characteristics.

A mathematical model using two forms of stochastic data has been developed by [Rappold 2011]. This is the only article that assumes a stochastic bill of materials for the procedures in an operating room. In addition, a stochastic demand is assumed. The authors developed a mathematical model using stochastic uncertainty and tested this using real data.

In most articles, models were developed considering uncertainty, however [Balcázar-Camacho 2016] and [Giuseppe 2016] developed a linear programming model for a distribution network. The proposed model considers a multi-echelon distribution system in which the objective function involves the minimization of the total costs.

Two exact models for lost sales and limited storage capacity have been developed by [Bijvank 2012]. In the capacity model, the service level is maximized subject to a capacity constraint; in the service model, the capacity required is minimized subject to a service level constraint. Authors developed a heuristic for the capacity model in which the re-order levels and order quantities are fixed. Another model that include storage constraints was developed in [Maestre 2018]. The proposed model is based on model predictive control to make decisions related to inventory levels of medicines applied in a hospital.

There are some other types of inventory models in hospitals that are not limited to medicines. [Diamant 2017] studied a problem in a hospital that outsources their sterilization services, the authors modeled the inventory process as a discrete-time Markov chain. They developed two base-stock inventory models: the first one considers stock-out-based substitution, and the second one doesn't consider it. The authors developed an analysis and varied the service level to determine the decisions related to inventories, stock-outs, and costs.

There are also some works that study the perishability of products in fields other than healthcare. For example in [Hengyu 2018] the perishability of agricultural foods is modeleded by using a surviving rate of product theta. Some experiments are carried out to measure the impact of the variation of this rate. Additionally, in [Janssen 2018] a perishable model for food waste is used and a simulation model is developed to validate and made a sensibility analysis. The proposed model considers the closing day's constraints and scenarios proves that saves up to 18% can be

obtained.

In addition, a reinforcement model based on age, considering a single product and a single echelon is developed in [Kara 2018]. The authors develop a method that can obtain a near-optimal solution considering the lead time and the life cycle as deterministic. A similar approach is developed in [Chaaben 2018] considering the life cycle as fixed or following an exponential distribution. Another approach is the study developed in [Rosa 2017] in which perishability is studied in production systems with delays in processes.

A pharmaceutical supply chain optimization model for crises events is presented in [Roshan 2019]. This model considers three different objective functions: costs, unmet demand and social responsibility. The authors proposed a MINLP model considering the uncertainty in the demand and the use of fuzzy logic, and they developed an auxiliary crisp model by using a triangular form. The model was tested by using a study case of Seattle. Another work that includes uncertainty as a fuzzy approach was developed in [Mousazadeh 2015] where authors proposed a mathematical model for mid-term decisions, such as a location-distribution problem in a network design.

An optimization model for a global pharmaceutical supply chain network is proposed in [Susarla 2012]. The authors propose the use of the production process in a multi-echelon, multi-side and multi-period problem. The proposed model is tested over data from a multinational company, and different types of configurations were assessed. [Meiler 2015] developed another planning model, where the authors proposed the use of a MILP model combined with network flow calculations.

Another approach based on a real case of the pharmaceutical industry is developed in [Amaroa 2008]. The proposed model contemplates the modeling of the scheduling and planning of pharmaceutical supply chains with reverse flows. The authors propose the use of a master representation of the supply chain at the operational level and a mathematical formulation to optimize the supply chain planning, connecting both problems with the use of bounds.

An application of simulation based optimization for a multi-objective problem is studied in [Caricato 2008]. The proposed approach is based on a real case study of the automotive sector where using a Pareto dominance concept, inefficient solutions are eliminated to provide only good quality solutions. Another application of simulation-based optimization in the design of energy efficient buildings is developed in [Sadik 2018]. Additionally, in [Mualla 2018], a multi-objective simulation-based optimization model is developed to solve the inventory replenishment problem with premium freights in convergent supply chains.

4.3 Methods

The simulation for optimization approach called the stochastic counterpart or sample path method discussed in [Fu 2002] and [Shapiro 1996] have been used. In this approach the simulation is the add-on used to generate scenarios for mathematical programming formulations. More specifically, a finite number of scenarios are generated, and the expected value function is approximated by the corresponding average function; this approximation is solved by classical optimization techniques. In a formal way, let the following objective function:

$$\min_{x \in \Theta} f(x) = \mathbf{E}[g(x, \xi)] \tag{4.1}$$

Where $x \in \Theta$ contains the input variables; $f(x)$ is the expected objective function value and ξ contains the random parameters. The approach previously mentioned consists in the generation of $\xi_1, \xi_2, ..., \xi_k$ independent realizations or scenarios that belong to the random vector ξ, and the objective function is approximated by:

$$\min_{x \in \Theta} \widehat{f(x)} = \frac{1}{K} \sum_{k=1}^{K} g(x, \xi_k) \tag{4.2}$$

The problem 4.2 becomes a deterministic optimization problem and is solved by using deterministic optimization techniques. Let $\widehat{z}_k$ and $\widehat{x}_k$ denote the optimal objective value and the optimal solution of problem 4.2, respectively. By the law of large numbers, $\widehat{z}_k$ converges to $f(x)$ w.p.1 as K $\to \infty$; therefore, $\widehat{z}_k$ and $\widehat{x}_k$ are consistent estimators of their "true" counterparts 4.1 [Shapiro 1996]. Based on this, Figure 4.1 presents the detailed methodology used in this study.

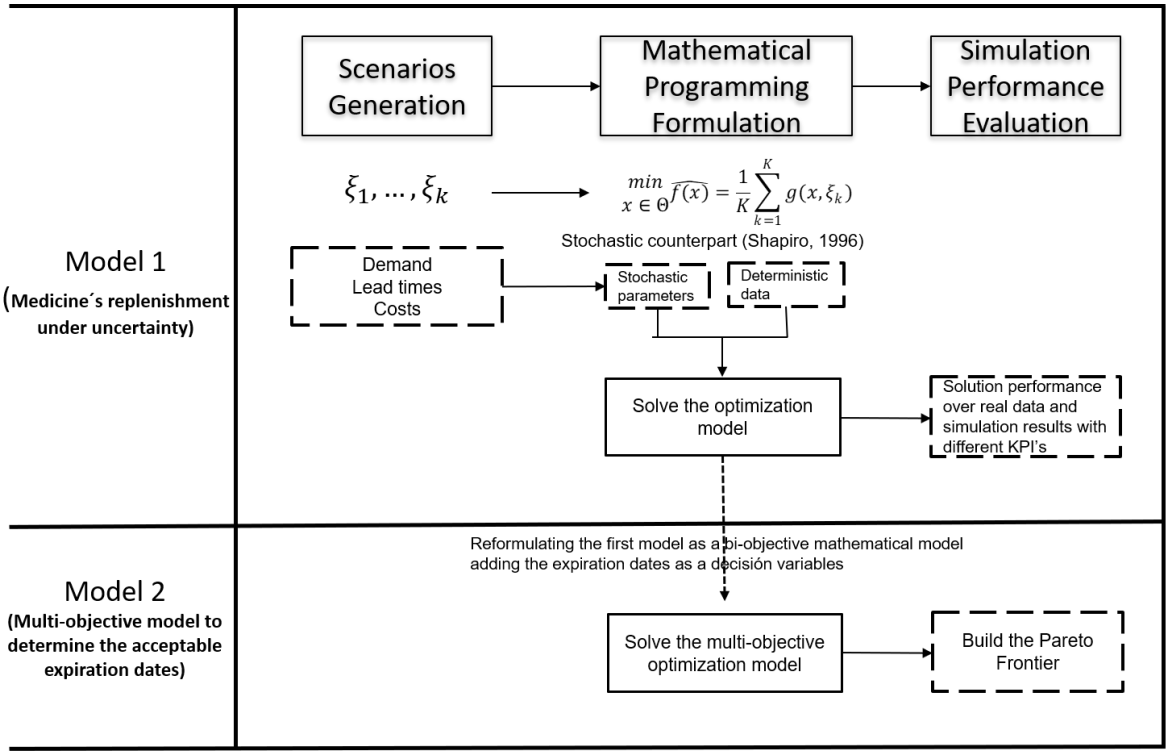

Figure 4.1: Methodology

The methodology presented in Figure 4.1 comprises: (i) the generation of a finite number of scenarios for random elements (Demand, Lead time and Costs of medicines), (ii) the mathematical programming formulation of two mixed integer programming (MIP) models, which correspond to the stochastic counterpart approximating problems for supply, replenishment and inventory management of medicines in the case of Model 1 and for decisions about expiration dates of medicines in the case of Model 2. The second model is proposed by adding the expiration date as a decision variable and by reformulating the problem as a bi-objective optimization model, which is solved by using the epsilon-constraint method. (iii) Using the values obtained through the generation of scenarios and the different parameters as inputs both models are solved to optimality. (iv) The final part of the methodology is the evaluation of the quality of solutions in a real case and the evaluation of the results of the proposed models for different indicators by using simulation for the first model and Pareto frontier for the second model.

4.4 Assumptions of the mathematical models

The main elements of the pharmaceutical supply chain are the following: (i) the suppliers that manufacture or distribute the medicines; (ii) the pharmacy that is in charge of ordering medicines from the suppliers, keeping the medicines safe, manag-

ing the inventory of medicines and distributing the medicines to the hospital; (iii) the hospital that provides medicines to patients and places orders from the pharmacy and finally (iv) the patients who require treatment and medicines (Figure 4.2).

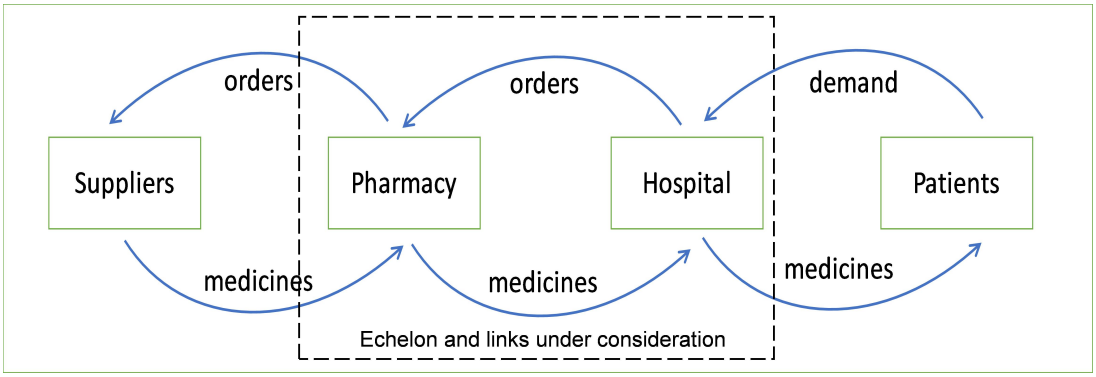

Figure 4.2: Interaction in the pharmaceutical supply chain

According to Figure 4.2, all decisions and actors in the chain deal with sources of uncertainty: Hospitals managers and pharmacies do not know the demand for the medicines, the pharmacy does not know the exact selling price of the medicines because the price can change over a planning horizon, and the lead times of suppliers are unknown to the pharmacy. In addition, the expiration dates are only known once the medicine arrives at the hospital. In this context, the sources of uncertainty are (i) demand, (ii) lead times and (iii) the costs of medicines (selling prices). Given the interaction of the echelons presented in Figure 4.2, the echelons and links of interest in this approach are highlighted; the main interest is to analyze the echelon of the pharmacy because it is the place where orders are placed to suppliers (where the decisions are taken). Based on this, the following assumptions are considered in this approach:

- Assumption A1: Each period time in T is one month.
- Assumption A2: The horizon planning is one year but it can be applied over higher horizons.
- Assumption A3: Lead time is positive, and it is modeled through the generation of scenarios.
- Assumption A4: The life cycle or expiration date is deterministic and known beforehand by the scenarios generated (only for the mathematical model 1).
- Assumption A5: The demand is modeled through the generation of scenarios.
- Assumption A6: Orders of medicines are placed by a number of lots because in hospitals, the requirements are not supplied by units of medicines or pills.

- Assumption A7: For each medicine, the initial stock = 0.
- Assumption A8: Orders are placed considering the lead time, except for the first period when the lead time is equal to 0; in this special case, this lead time is relaxed to avoid infeasibility.
- Assumption A9: The received order is placed with age = 1.
- Assumption A10: Quantification of expired medicines are modeled through the classical inventory level constraints taking into account the life cycle of medicines in order to consider the traceability requirements of medicines determined by Colombian law 0371/2009, therefore, medicines with different remaining times are used to satisfy the demand, decreasing the inventory levels for the specified remaining time.
- Assumption A11: Given the Colombian regulation (resolutions 1896/2001 and 1604 2013), the demand of medicines must be satisfied with a 100% of service level. In case that inventory is not enough to satisfy the demand, an emergency purchase is made to satisfy it, and the price of the medicine is higher than its regular purchase price.
- Assumption A12: There is no lead time for the emergency purchase; thus, once the purchase is required, the medicine arrives to satisfy the demand.
- Assumption A13: Figure 4.3 outlines the structure of the decisions, the uncertainty and the information available in the horizon planning. In this example, once a decision to purchase is made in a specific period time, the cost of medicine is determined for this specific period time. This is because the selling price is a random element and changes in every period of time. In addition, the lead times of medicines are random elements. Once the medicine arrives, it can be used to satisfy the demand and/or kept in inventory by using the age-based inventory constraints and the age of medicines to model the perishability. After a number of cycles, some medicines are expired because of their age; therefore, if there is not enough quantity of medicines on inventory to satisfy the demand that is a random element too, an emergency purchase can be made to satisfy the demand, but the purchase will be made at a higher price.
- Assumption A14: Constraints of the mathematical model were built based on the underlying event dynamics of the system. The demand pulls the system reducing the inventory level of medicines. The decisions of regular and emergency purchases are influenced by the inventory level ($IL \geq 0$ or $IL \leq 0$) and the expired medicines. Once a decision is made, medicines arrive with a lead time updating the inventory level. In this way decisions of regular and emergency purchases are feasible overall scenarios allowing the generation of a common policy of purchases.

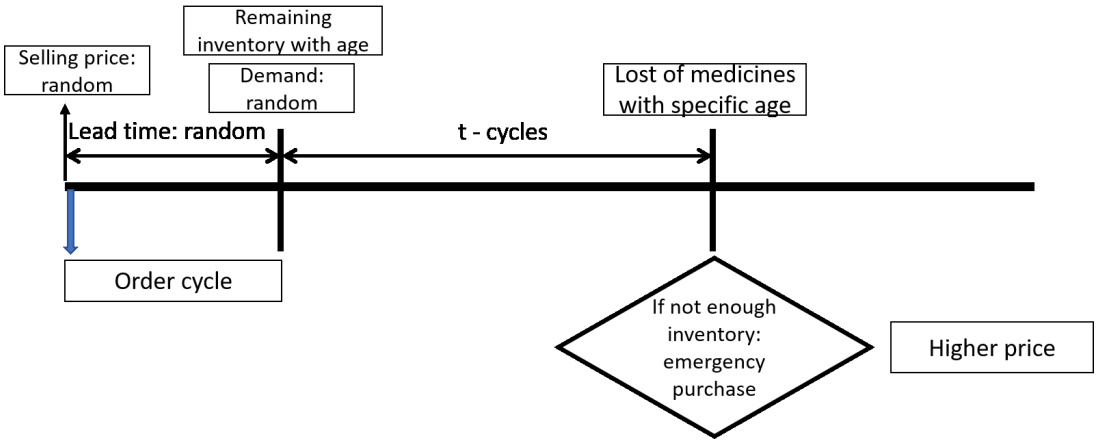

Figure 4.3: Structure of decisions

- Assumption A15: In this approach, the mathematical models are focused on the decisions taken by the pharmaceutical area that belongs to the hospital. In the context of this study, the hospital is in charge of patients, and the responsibility of managing medicines is the responsibility of the pharmacy area

4.5 Mathematical Model 1: Medicine's replenishment under uncertainty

Sets

N	Time periods in the planning horizon
P	Type of medicines
S	Suppliers
L	Set of medicine's age
K	Scenarios of the random vector

Random numbers

d_{ptk}	Demand of medicine type p in period t in scenario k
lt_{spk}	Lead time of supplier s for medicine p in scenario k
c_{sptk}	Cost of medicine p by the supplier s in period t in scenario k

cl_{psk}	Cost of expired medicine p from supplier s in scenario k

Parameters

ls_p	Lot size of medicine type p
av_{sp}	$\begin{cases} 1 \text{ if the supplier s sells the medicine p} \\ 0, \text{ otherwise} \end{cases}$
ut_p	Unitary time for making unit doses for medicine p
lc_p	Shelf life of medicine p
ec_p	Emergency cost of medicine p
cap	Human resource capacity (in hours per month)
mna	Maximum number of orders of different types of medicines

Variables

Q^s_{pt}	Number of lots of medicine p in period t placed to supplier s
y^s_{pt}	$\begin{cases} 1 \text{ if the requirement of medicine p to supplier s in period t is placed} \\ 0, \text{ otherwise} \end{cases}$
IP^{lk}_{pt}	Inventory level of medicine p with life cycle l in time t in scenario k
I^k_{pt}	Inventory level of medicine p in time t in scenario k
RP^{lk}_{pt}	Amount of medicine p of life cycle l administrated to patients in time t in scenario k
R^k_{pt}	Total amount of medicine p administrated to patients in time t in scenario k
EQ_{pt}	Number of lots of medicine p purchased in case of emergency in period time t

The model proposed is formulated over a planning horizon T, where $|T|$=12 and each time period correspond to one month where also each medicine has it own shelf life L, where $|L|$=12. In each month for each type of medicine $p \in P$ there is a demand d_{ptk} that is generated by using a set K of scenarios. The requirement of medicines are satisfied by a set of suppliers S where the parameter av_{sp} indicates if the supplier sells the medicine $p \in P$. In addition, each supplier s has its own lead

times lt_{spk} that is generated by using a set of scenarios K. Each type of medicine has its shelf life or expiration date determined by lc_p.

There are two main variables denoting the medicines' requirements, Q^s_{pt} and EQ_{pt}. The first variable determines the lots of medicines to request to a specific supplier, this requirement is related with the parameter ls_p that determines the number of medicines in each lot. Once a purchase is completed, the amount of medicines increases the inventory-based age constraints with the respective age L (where each age increases in months; age 1= 1 month, age 2 = to months, and so on) in IP^{lk}_{pt}. These purchases are made with a random cost c_{sptk}. The variable RP^{lk}_{pt} defines the quantities of medicines that are taken from inventory levels to satisfy the demand. In case there is not enough quantity of medicines to satisfy the demand, the variable EQ_{pt} determines the quantity of medicines that are purchased in case of emergency to satisfy the demand, this purchase is made with a cost ec_p where $ec_p > c_{sptk}$. They are also request in terms of lots ls_p.

The maximum number of orders allowed in each period time is defined by mna. To satisfy this constraint, the binary variable y^s_{pt} is used to determine if in a specific period of time, an order of medicine to a specific supplier will be launched. Another type of administrative constraint is modeled considering the number of human resources available per period time, which is defined by cap. To model this constraint, the parameter ut_p that indicates the consumption of time in hours to prepare a unit-doses is used.

Objective

The objective function minimizes the expected total costs over all scenarios. It contains the costs of regular purchases, the costs of emergency purchases and the costs of expired medicines (readers should note the inventory holding cost is not included directly, but it can be estimated through the use of the expired medicines, according to [Ghiani 2004] and is defined by the obsolescence costs).

$$Min\ z = \frac{1}{|K|}\left(\sum_{k\in K}\sum_{t\in T}\sum_{s\in S}\sum_{p\in P} c_{sptk} * Q^s_{pt} + |K| \sum_{t\in T}\sum_{p\in P} ec_p * EQ_{pt} + \sum_{s\in S}\sum_{k\in K}\sum_{t\in T}\sum_{p\in P}\sum_{l\in L|(t-l)>lt_{spk}-1} cl_{psk} * IP^{lk}_{pt}\right)$$

Constraints

In this formulation, the age of medicines is modeled by using the shelf life in order to consider the traceability requirements of medicines determined by the Colombian law 0371 2009. Based on this, two different types of constraints are built (1 and 2).

1. The aged inventory for each scenario, for each type of medicine and for each life cycle is defined. This means that in a time period, there are amounts of the same medicine that have different life cycles. Thus, the constraints in a specific time period for a specific medicine of a specific life cycle is equal to the amount of medicine in the previous period that has one period less of life cycle minus the

amount of medicine used to satisfy the demand with any specific life cycle. Then, the age of medicine used to satisfy the demand can be selected.

$$IP_{pt}^{lk} = IP_{pt-1}^{l-1k} - RP_{pt-1}^{lk} \qquad \forall t, \forall p, \forall l | l \leq t \, and \, t - l \leq lc_p - 1, \forall k$$

2. This constraint is complementary to constraint 1 because it establishes that when a purchase is made the life cycle of the medicine is one; in this way the life cycle of medicines when they increase the period of life can be modeled. Also, the amount of medicines is multiplied by the lot size. Finally, the amount of medicines with a life cycle of one given to satisfy the demand is subtracted.

$$IP_{pt}^{lk} = \sum_{s \in S} ls_p * Q_{pt-lt_{spk}}^{s} - RP_{pt}^{lk} \qquad \forall t, \forall p, \forall l = 1, \forall k$$

3. The net inventory for a specific type of medicine in every time period in each scenario is equal to the total amount of medicines in a specific time period in a specific scenario for each type of medicine.

$$I_{pt}^{k} = \sum_{l \in 1..t} IP_{pt}^{lk} \qquad \forall t, \forall p, \forall k$$

4. Similar to constraint 3, the amount of medicines distributed to satisfy the demand is totalized.

$$R_{pt}^{k} = \sum_{l \in 1..t} RP_{pt}^{lk} \qquad \forall t, \forall p, \forall k$$

5. Guarantee that it is only possible to purchase medicines if the binary variable y_{pt}^{s} is activated.

$$Q_{pt}^{s} \leq M * y_{pt}^{s} \qquad \forall t, \forall p, \forall s$$

6. The availability of medicines is modeled as the relationship between the binary variable that defines if a specific amount of medicine is supplied by a specific company and the parameter that indicates if the company has in its portfolio a specific medicine.

$$y_{pt}^{s} \leq av_{sp} \qquad \forall t, \forall p, \forall s$$

7. By Colombian regulation (1403/2007), every medicine must be put in unit-dose packages; therefore, preparation of unit-dosesâ times and the capacity of regents of pharmacy must be taken into account in the models. The unitary time for each type of medicine is multiplied by the amount of medicines (lot size multiplied by the quantity of lots requested from companies); this amount cannot exceed the capacity of personnel involved in this task.

$$\sum_{p \in P} \sum_{s \in S} ut_p * ls_p * Q_{pt}^s \leq cap \qquad \forall t$$

8. Given the Colombian regulation (resolutions 1896/2001 and 1604 2013), the demand of medicines must be satisfied with a 100% of service level; therefore, the hospital is not allowed to have backorders or shortages because of the potential for negative impacts on the health of patients. Thus, if there is not enough medicine in inventory, an emergency purchase is made, but the cost of each medicine increases.

$$R_{pt}^k + ls_p * EQ_{pt} = d_{ptk} \qquad \forall t, \forall p, \forall k$$

9. A different type of human capacity constraint is modeled in this equation. Given the high number of products, suppliers and administrative procedures related to the purchase of medicines usually conducted by a single professional, it is not allowed to request all medicines in each period of time.

$$\sum_{p \in P} \sum_{s \in S} y_{pt}^s \leq mna \qquad \forall t$$

10. Medicines with ages that are higher than its perishable date cannot be distributed to patients.

$$RP_{pt}^{lk} = 0 \qquad \forall t, \forall p, \forall l | t - l > lc_p - 1, \forall k$$

11. The bound of variables are modeled by the following equations.

$$\begin{aligned}
Q_{pt}^s \geq 0 \qquad & \forall t, \forall p, \forall s \\
IP_{pt}^{lk} \geq 0, RP_{pt}^{lk} \geq 0 \qquad & \forall t, \forall p, \forall l, \forall k \\
R_{pt}^k \geq 0, I_{pt}^k \geq 0 \qquad & \forall t, \forall p, \forall k \\
EQ_{pt} \geq 0 \qquad & \forall t, \forall p \\
Q_{pt}^s, I_{pt}^k, RP_{pt}^{lk}, R_{pt}^k, IP_{pt}^{lk}, EQ_{pt} \in \mathbb{Z} & \\
y_{pt}^s \in \{0, 1\} &
\end{aligned}$$

The mathematical model for medicine's replenishment under uncertainty is summarized as follows:

$$Min\ z = \frac{1}{|K|}\left(\sum_{k\in K}\sum_{t\in T}\sum_{s\in S}\sum_{p\in P} c_{sptk} * Q^s_{pt} + |K|\sum_{t\in T}\sum_{p\in P} ec_p * EQ_{pt} + \sum_{s\in S}\sum_{k\in K}\sum_{t\in T}\sum_{p\in P}\sum_{l\in L|(t-l)>lt_{spk}-1} cl_{psk} * IP^{lk}_{pt}\right) \tag{4.3}$$

Subject to:

$$IP^{lk}_{pt} = IP^{l-1k}_{pt-1} - RP^{lk}_{pt} \qquad \forall t, \forall p, \forall l | l \leq t\ and\ t - l \leq lc_p - 1, \forall k \tag{4.4}$$

$$IP^{lk}_{pt} = \sum_{s\in S} ls_p * Q^s_{pt-lt_{spk}} - RP^{lk}_{pt} \qquad \forall t, \forall p, \forall l = 1, \forall k \tag{4.5}$$

$$I^k_{pt} = \sum_{l\in 1..t} IP^{lk}_{pt} \qquad \forall t, \forall p, \forall k \tag{4.6}$$

$$R^k_{pt} = \sum_{l\in 1..t} RP^{lk}_{pt} \qquad \forall t, \forall p, \forall k \tag{4.7}$$

$$Q^s_{pt} \leq M * y^s_{pt} \qquad \forall t, \forall p, \forall s \tag{4.8}$$

$$y^s_{pt} \leq av_{sp} \qquad \forall t, \forall p, \forall s \tag{4.9}$$

$$\sum_{p\in P}\sum_{s\in S} ut_p * ls_p * Q^s_{pt} \leq cap \qquad \forall t \tag{4.10}$$

$$R^k_{pt} + ls_p * EQ_{pt} = d_{ptk} \qquad \forall t, \forall p, \forall k \tag{4.11}$$

$$\sum_{p\in P}\sum_{s\in S} y^s_{pt} \leq mna \qquad \forall t \tag{4.12}$$

$$RP^{lk}_{pt} = 0 \qquad \forall t, \forall p, \forall l | t - l > lc_p - 1, \forall k \tag{4.13}$$

$$
\begin{aligned}
Q^s_{pt} \geq 0 \qquad & \forall t, \forall p, \forall s \\
IP^{lk}_{pt} \geq 0, RP^{lk}_{pt} \geq 0 \qquad & \forall t, \forall p, \forall l \forall k \\
R^k_{pt} \geq 0, I^k_{pt} \geq 0 \qquad & \forall t, \forall p, \forall k \\
EQ_{pt} \geq 0 \qquad & \forall t, \forall p \\
Q^s_{pt}, I^k_{pt}, RP^{lk}_{pt}, R^k_{pt}, IP^{lk}_{pt}, EQ_{pt} \in \mathbb{Z} & \\
y^s_{pt} \in \{0,1\} & \qquad (4.14)
\end{aligned}
$$

4.5.1 Experimental setting

Real data provided by a private Colombian hospital was used and the following information were analyzed: supplier selling prices, lead times , shelf life and demand of medicines as well as the emergency purchases and their prices, lot size of medicines and time requirements for making unit-doses. The model was tested over a planning horizon divided in 12 time periods with the 22 medicines with higher demand, 10 suppliers (taken directly of the real information of the hospital) and 30 scenarios in order to get a reasonable computational time and guarantee an estimated gap <1% [Shapiro 2008] (see subsection 4.5.2).

As it is considered three different sources of uncertainty (demand, lead times and costs of medicines), it has been used different approximations to generate the different scenarios as follows:

- Demand of medicines (d_{ptk}). The demand is generated according to a non-homogenous Poisson process because for each time period, the increments are not stationary as it is concluded by the Mann Kendall and Laplace temporal trend tests performed for all medicines under analysis (30 observations for each medicine with a confidence of 95% (see Appendix A). Each scenario k of demand for each type of medicine is built through the implementation of the piecewise thinning algorithm [Ross 1997]. Each scenario k is composed by the demand generated for each time period.

Given the number of combinations of supplier and medicines, the scenarios for lead times and costs of medicines were generated according to a specific criteria: a common distribution for each random variable with different parameters for each combination. A goodness of fit test was performed for all possible combinations (not all suppliers sell all types of medicines). The uniform distribution (continuous for cost of medicines and discrete for lead times) was ranked always in the first three positions. For this reason, all combinations of suppliers and medicines were fitted to a discrete uniform distribution for lead times and a uniform distribution for cost of medicines. For both random variables a goodness of fit was successfully passed with confidence of 95 % for all combinations (not all suppliers sell all types of medicines, see Appendix A).

- Lead time of medicines (lt_{spk}). For the lead times, the number of time periods required for delivering medicines for each supplier and for each medicine is counted. With this information it was analyzed the ranges of lead times. Each scenario k of lead time for each supplier s and each medicine p is generated by a random number generator for the discrete uniform distribution.

- Cost of medicines (c_{sptk}). The range of selling prices for each type of supplier and for each type of medicine has been analyzed. Each scenario k of cost for each type of medicine, each type of supplier and for each time period is generated by a random number generator for the uniform distribution. Also, for the cost of expired medicine (cl_{psk}), it has been generated scenarios by a random number generator for the uniform distribution.

4.5.2 Results and analysis

Based on the information provided by the hospital, different sample sizes of scenarios have been generated, for each one of the random elements: medicine demand, lead time and costs for each time period. The model have been run over a planning horizon divided into 12 time periods (months). The mathematical model 1 (eq. 4.3 to eq. 4.14) is solved to optimality by using Xpress-MP, version 8.1.

Depending on the number of scenarios the estimated gap and variance of solution obtained are calculated iteratively, based on the framework proposed in [Shapiro 2008] which estimates an upper bound and a lower bound of the objective function, this allows to identify the variance obtained and the optimality gap with respect to the estimation of the value of the objective function. The gap is defined as the difference (in percentage) between the upper bound and the lower bound, therefore the gap is the difference between the estimation of the objective function and the value of the real objective function.

The procedure consists in determine the average solution of the scenarios by using:

$$\frac{1}{M}\sum_{m=1}^{M} g_M^m \tag{4.15}$$

Where M correspond to the scenarios generated and g_M^m the objective function of each scenario. The variance is estimated throw:

$$\frac{1}{m(m-1)}\sum_{m=1}^{M}(g_M^m - \overline{g_M^m})^2 \tag{4.16}$$

Where $\overline{g_M^m}$ corresponds to the average of the objective functions, and the confi-

dence upper bound: $g_M^m + \theta_{\alpha,M-1} * variance$ that corresponds to the upper bound of the approximation of the objective function. Then, by using the same calculations and larger scenarios N a lower bound of the objective function is estimated with $g_N^n + z_\alpha * variance_2$ and the gap comparing these two bounds are obtained with $g_M^m + \theta_{\alpha,M-1} * variance$ - $g_N^n + z_\alpha * variance_2$.

According to this procedure, first 4 and 8 scenarios are tested for estimating the lower and upper bounds respectively, in this first iteration the gap obtained is 18.63%. For the second iteration 8 and 16 scenarios are tested obtaining a gap of 1.84%. Finally, 30 and 60 scenarios are tested obtaining a gap of 0.85%, which is a satisfactory value of estimation.

The results for the inventory levels for 22 medicines are presented in Figure 4.4. The figure shows the inventory levels in units for 12 months for each type of medicine.

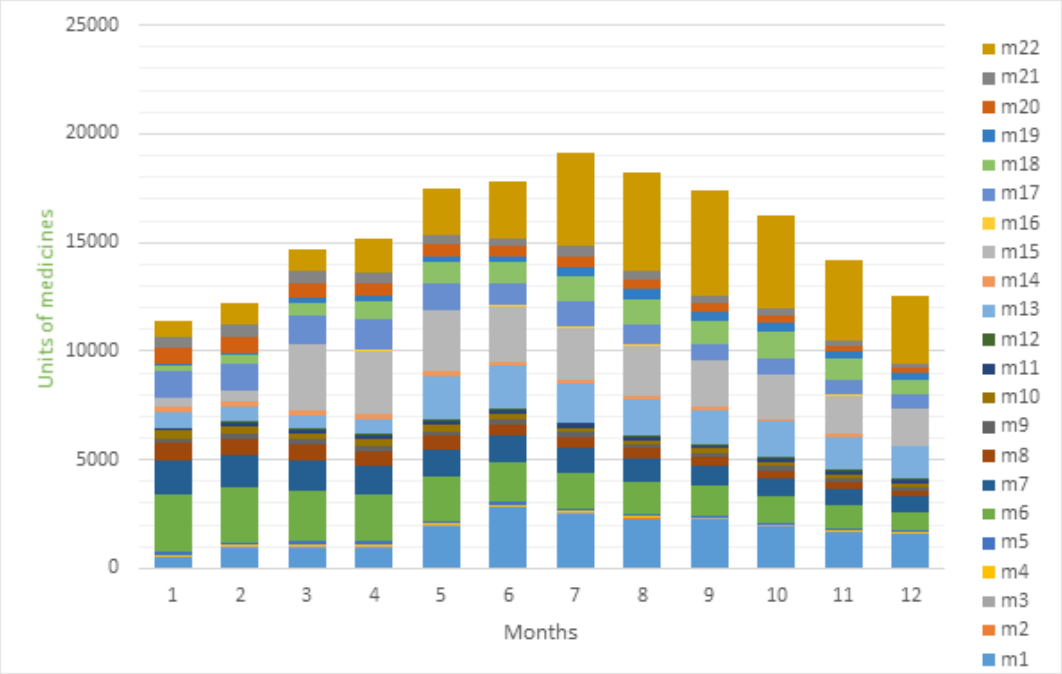

Figure 4.4: Inventory levels for each type of medicine in each time period

It can be observed in Figure 4.4 that inventory levels are balanced during the planning horizon; in other words, the inventory levels are greater than 0 in each month, and there are not any periods in which there are medicines with inventory levels equal 0 and other medicines with higher inventory levels. This is due to the capacity constraints modeled by the equation 4.10 and 4.12 which limit the quantities that can be purchased from the suppliers; the demand varies in each time period. In addition, two different indicators have been analyzed: the first one

corresponds to the total amount of emergency purchases made during the planning horizon, and the second one corresponds to the total amount of expired medicines. (Table 4.1).

Medicine	Emergency purchases (number of medicines)	Expired medicines (number of medicines)
m1	144	0
m2	32	0
m3	11	16
m4	11	6
m5	16	0
m6	721	0
m7	121	0
m8	30	0
m9	0	0
m10	49	0
m11	0	42
m12	0	0
m13	0	0
m14	14	0
m15	26	28
m16	1	0
m17	120	0
m18	139	0
m19	75	0
m20	75	0
m21	116	0
m22	12	0

Table 4.1: Total emergency purchases and expired medicines

In Table 4.1, it can be observed that for 4 different types of medicines (m9, m11, m12 and m13), emergency purchases are never made. For the rest of the medicines, the maximum value for the number of emergency purchases comprises 721 units for medicine 6. In addition, it can be observed that among the different medicines, the amount of expired medicines does not represent a large number. Only 4 types of medicines expired (m3, m4, m11 and m15), corresponding to 18% of the medicines. For the expired medicines, the maximum value, 42 units, was for medicine 11.

Under similar conditions it is compared (taking into account the real data of hospital), the optimal policy obtained by the model proposed (eq. 4.3 to eq. 4.14) with the policy used by the hospital. These results are summarized in Table 4.2 (For confidential reasons the results are presented in cost units (CU)); for each medicine,

the first data column displays the cost (CU) associated with the decisions of the hospital for each medicine, the second column presents the cost in CU associated with the optimal policy obtained from the mathematical model (defined as C-policy), and the third column presents the difference between these two values.

Medicine	Real (CU)	C-policy (CU)	Difference (%)
m1	624	602	3.58%
m2	942	472	49.91%
m3	537	488	9.26%
m4	1129	1126	0.26%
m5	24	21	11.48%
m6	2927	2987	-2.07%
m7	36	26	28.24%
m8	367	276	24.77%
m9	64	57	11.06%
m10	524	540	-3.11%
m11	156	121	22.19%
m12	592	431	27.24%
m13	312	202	35.28%
m14	5716	5834	-2.07%
m15	780	724	7.15%
m16	1312	785	40.15%
m17	966	1084	-12.24%
m18	76	75	1.24%
m19	93643	74230	20.73%
m20	16309	16372	-0.39%
m21	5431	5023	7.52%
m22	211	160	23.96%
Total	**132675**	**111634**	**15.86%**

Table 4.2: Comparison between real situation and optimal policy

It can be concluded that for most of the medicines (17), the optimal policy obtained from the mathematical model improves the supply policy in the hospital. Considering the 22 medicines, it is possible to reduce the total costs of the managing of medicines by 15.86%. For 17 of the 22 medicines there was a reduction of costs of 20.16%, representing a savings of $85667 US dollars. For 5 medicines there was an increase of costs of 1.42%, representing an increase of $1505 US dollars.

4.5.3 Simulation analysis

416 scenarios of the random elements have been simulated: demand, lead times and costs, for each one of the 22 different types of medicines in order to evaluate the

performance of the optimal policy obtained by the mathematical model (eq. 4.3 to eq. 4.14) over these scenarios. The results are shown in Table 4.3.

	Scenarios with stockout (number of scenarios)	Average Stockout (units)	Average Inventory Levels (units)
m1	179	86.52	2683.89
m2	0	0.00	161.01
m3	185	1.07	28.06
m4	416	19.98	7.48
m5	267	7.56	74.31
m6	0	0.00	2351.83
m7	0	0.00	1236.22
m8	0	0.00	583.22
m9	409	22.94	7.73
m10	0	0.00	290.57
m11	416	30.12	2.91
m12	393	7.91	8.36
m13	416	53.26	16.72
m14	339	19.42	100.67
m15	327	46.05	534.14
m16	0	0.00	41.25
m17	0	0.00	1153.79
m18	0	0.00	1155.47
m19	0	0.00	358.12
m20	0	0.00	760.23
m21	0	0.00	1002.36
m22	85	20.10	2612.60

Table 4.3: Optimal policy performance over the simulated scenarios

The results presented in Table 4.3 correspond to three different key performance indicators: (i) the number of scenarios with stockout, which in this case corresponds to the emergency purchases, (ii) the average number of stockouts and (iii) the average inventory levels. In the first case, in 50% of the medicines, the results provided by the mathematical model allow not having stockouts, thereby minimizing the total costs of emergency purchases for medicines. This analysis is related to the second key performance indicator: for the 12 medicines that contain scenarios with stockouts, the average number of stockouts is 26.25 units. In the current situation of the hospital, the number of emergency purchases for some medicines can be greater than 300 units, the optimal policy obtained by the model allows reduce the emergency

purchases which can be up to 500% of the regular value. Inventory levels are on average consistent with those presented in Figure 4.4.

Finally, in Figure 4.5, the comparison of the three indicators (the total amount of inventory levels, the total amount of expired medicines and the total amount of emergency purchases) is developed with the results of the three policies: the hospital policy, the optimal policy evaluated over the real data and the optimal policy evaluated over the simulated data.

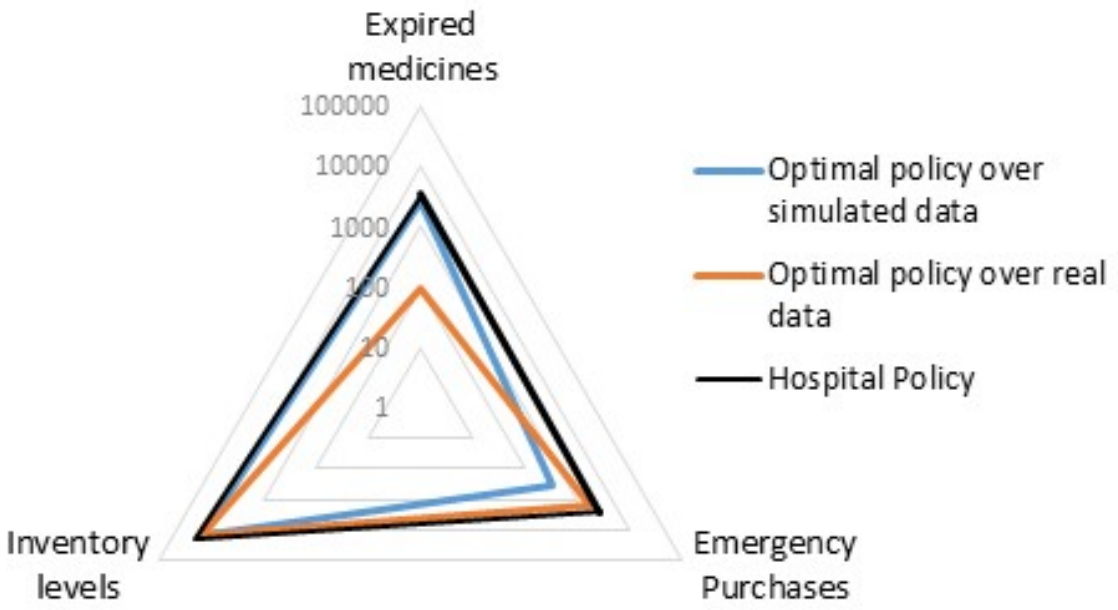

Figure 4.5: Comparison of policies

Note that for the optimal policy evaluated on both real and simulated data all three indicators: inventory levels, total of the expired medicines and emergency purchases are lower than the hospital policy (R,Q). For this reason, with the mathematical model, the replenishment decisions can be improved in terms of costs of inventory management, expired medicines management and emergency purchases management. The results can be used as an input of the ERP system supporting decision of purchases allowing a reduction of emergency purchases and expired medicines.

4.6 Multi-objective model to determine the acceptable expiration dates

Another problem faced by the hospital is the amount of expired medicines. The expiration date is only known when the medicines are received, not during negotiations for the supply. For this reason, considering the uncertainties mentioned above, it is important to determine an acceptable expiration date for each type of medicine. Based on the previous model and with the main objective of determining the maximum expiration date medicines should have for the hospital to accept them and for minimizing the number of expired medicines, a second mathematical model have been developed where the objective is composed of two different objective functions that contrast the amount of expired medicine with the expiration date obtained by the model.

To develop the second mathematical model, two new decision variables, z_{pj}^{t} and QF_{pt}^{lk} are introduced:

Variables

z_{pj}^{t} $\begin{cases} 1 \text{ if in the time period t,medicine with expiration date j is accepted where j} \in \text{T} \\ 0 \text{ otherwise} \end{cases}$

QF_{pt}^{lk} Quantity of medicine p with age l $\in$ L expired in time period t in scenario k

Objective functions

1. Value of the expiration date

$$Min\, z1 = \sum_{p \in P} \sum_{j \in T | j \geq t} \sum_{t \in T} (l - t) * z_{pj}^{t}$$

2. The amount of expired medicines

$$Min\, z2 = \frac{1}{|K|} \sum_{p \in P} \sum_{k \in K} \sum_{l \in L} \sum_{t \in T} QF_{pt}^{lk}$$

New constraints

1. Inventory levels including the expired medicines

$$IP_{pt}^{lk} = IP_{pt-1}^{l-1k} - RP_{pt}^{lk} - QF_{pt}^{lk} \qquad \forall t, \forall p, \forall l | l \leq t, \forall k$$

$$IP_{pt}^{lk} = \sum_{s \in S} ls_p * Q_{pt-lt_{spk}}^{s} - RP_{pt}^{lk} - QF_{pt}^{lk} \qquad \forall t, \forall p, \forall l = 1, \forall k$$

2. Each lot of medicine has an unique expiration date

$$\sum_{j \in T | j \geq t} z_{pj}^{t} \leq 1 \qquad \forall t, \forall p$$

3. If the expiration date of medicines is not established, an order for medicines cannot be placed

$$Q_{pt}^{s} \leq M * \sum_{j \in T} z_{pj}^{t} \qquad \forall t, \forall p, \forall s$$

4. The following equations represent the age based constraints. To guarantee the relationship between the quantity of expired medicines and the binary variable z_{pj}^{t}. It establishes that when the value of the binary variable is one, it determines the end of life for a certain type of medicine; then, when this age is reached, the amount of expired medicines is equal to the inventory of medicines with the same age. For example, $z_{32}^{4} = 1$ indicates that a lot of medicine 3 is accepted in period 2 and expires in period 4 (therefore, the age will be 3 months in period 4); the amount of medicines expired is represented by $QF_{34}^{(t2-l+1)k}$, where (t2-j+1)=(4-2+1)=3 and the amount of inventory subtracted is IP_{34}^{3k}, denoting a relationship in which the quantity expired will be the amount of inventory accepted in a previous period of time with a specific expiration date. In addition, in a specific time period, there is only one possibility for a specific age; for example, in period t=5, a medicine with age l=3 is the medicine whose purchase was made two previous periods earlier in period t=3. When the binary variable is activated, the amount of expired medicines has two bounds:

The lower bound

$$QF_{pt}^{(t2-j+1)k} \geq IP_{pt}^{(t2-j+1)k} - M*(1-z_{pj}^{t2}) \qquad \forall t, \forall p, \forall j | j \leq t, \forall t2 \in T | t2 \geq j, t2 = 1...t, \forall k$$

The upper bound:

$$QF_{pt}^{(t2-j+1)k} \leq IP_{pt}^{(t2-j+1)k} \qquad \forall t, \forall p, \forall j | j \leq t, \forall t2 | t2 \leq j, t2 = 1...t, \forall k$$

5. The bound of variables are modeled by the following equations

$$QF_{pt}^{lk} \geq 0 \qquad \forall t, \forall p, \forall l, \forall k$$
$$Q_{pt}^{s} \geq 0 \qquad \forall t, \forall p, \forall s$$
$$IP_{pt}^{lk} \geq 0, RP_{pt}^{lk} \geq 0 \qquad \forall t, \forall p, \forall l, \forall k$$
$$QF_{pt}^{lk}, IP_{pt}^{lk}, RP_{pt}^{lk}, Q_{pt}^{s} \in \mathbb{Z}$$
$$z_{pj}^{t} \in \{0, 1\}$$

The multi-objective mathematical model for acceptable expiration dates under uncertainty contains the above equations and the equations 4.6- 4.14 of the first model(Section 4.5). This model can be summarized as follows:

$$Min\ z1 = \sum_{p \in P} \sum_{j \in T | j \geq t} \sum_{t \in T} (l - t) * z_{pj}^{t} \tag{4.17}$$

$$Min\ z2 = \frac{1}{|K|} \sum_{p \in P} \sum_{k \in K} \sum_{l \in L} \sum_{t \in T} QF_{pt}^{lk} \tag{4.18}$$

Subject to:

$$IP_{pt}^{lk} = IP_{pt-1}^{l-1k} - RP_{pt}^{lk} - QF_{pt}^{lk} \qquad \forall t, \forall p, \forall l | l \leq t, \forall k \tag{4.19}$$

$$IP_{pt}^{lk} = \sum_{s \in S} ls_p * Q_{pt-lt_{spk}}^{s} - RP_{pt}^{lk} - QF_{pt}^{lk} \qquad \forall t, \forall p, \forall l = 1, \forall k \tag{4.20}$$

$$\sum_{j \in T | j \geq t} z_{pj}^{t} \leq 1 \qquad \forall t, \forall p \tag{4.21}$$

$$Q_{p_t}^{s} \leq M * \sum_{j \in T} z_{pj}^{t} \qquad \forall t, \forall p, \forall s \tag{4.22}$$

$$QF_{pt}^{(t2-j+1)k} \geq IP_{pt}^{(t2-j+1)k} - M*(1-z_{pj}^{t2}) \qquad \forall t, \forall p, \forall j | j \leq t, \forall t2 \in T | t2 \geq j, t2 = 1..t, \forall k \tag{4.23}$$

$$QF_{pt}^{(t2-j+1)k} \leq IP_{pt}^{(t2-j+1)k} \qquad \forall t, \forall p, \forall j | j \leq t, \forall t2 | t2 \leq j, t2 = 1...t, \forall k \tag{4.24}$$

$$I_{pt}^{k} = \sum_{l \in 1..t} IP_{pt}^{lk} \qquad \forall t, \forall p, \forall k \tag{4.25}$$

$$R_{pt}^{k} = \sum_{l \in 1..t} RP_{pt}^{lk} \qquad \forall t, \forall p, \forall k \tag{4.26}$$

$$Q_{pt}^{s} \leq M * y_{pt}^{s} \qquad \forall t, \forall p, \forall s \tag{4.27}$$

$$y_{pt}^{s} \leq av_{sp} \qquad \forall t, \forall p, \forall s \tag{4.28}$$

$$\sum_{p \in P} \sum_{s \in S} ut_p * ls_p * Q_{pt}^{s} \leq cap \qquad \forall t \tag{4.29}$$

$$R_{pt}^{k} + ls_p * EQ_{pt} = d_{ptk} \qquad \forall t, \forall p, \forall k \tag{4.30}$$

$$\sum_{p \in P} \sum_{s \in S} y_{pt}^{s} \leq mna \qquad \forall t \tag{4.31}$$

$$RP_{pt}^{lk} = 0 \qquad \forall t, \forall p, \forall l | t - l > lc_p - 1, \forall k \tag{4.32}$$

$$\begin{aligned} QF_{pt}^{lk}, IP_{pt}^{lk} \geq 0, RP_{pt}^{lk} \geq 0 \qquad & \forall t, \forall p, \forall l, \forall k \\ I_{pt}^{k} \geq 0, R_{pt}^{k} \geq 0 \qquad & \forall t, \forall p, \forall k \\ Q_{pt}^{s} \geq 0 \qquad & \forall t, \forall p, \forall s \\ EQ_{pt} \geq 0 \qquad & \forall t, \forall p \\ QF_{pt}^{lk}, IP_{pt}^{lk}, RP_{pt}^{lk}, I_{pt}^{k}, R_{pt}^{k}, Q_{pt}^{s}, EQ_{pt} \in \mathbb{Z} & \\ z_{pj}^{t}, y_{pt}^{s} \in \{0, 1\} & \end{aligned} \tag{4.33}$$

4.6.1 Results and analysis

To determine the maximum expiration date medicines should have for the hospital to accept them, for each medicine, two objective functions were formulated (equations 4.17 and 4.18). These two objectives are contradictory because the minimum expiration date is 0, but there will be an increment in the expired medicines and the maximum expiration date is 12 (months), where there will be a minimization of expired medicines. To solve this situation the epsilon-constraint strategy have been used [Haimes 1971] for each type of medicine. The procedure consists of optimizing

each objective function separately, with the objective of finding the two extreme points of the Pareto frontier.

In Figure 4.6 it can observed the results of the model for a single type of medicine (3). The solution presented can be used by decision makers to accept a reasonable expiration date. It is clear that the ideal solution is that the amount of expired medicines will be zero. This can occur with a long expiration date, in this case 12 months, which is the same as the planning horizon. As mentioned before, the expiration dates are only known when the product is delivered by suppliers, but in this case, for negotiation, hospitals can refuse to accept the medicines if the expiration date is not appropriate for the objectives of the hospital. This solution can give to the hospital an initial idea of the acceptable date of expiration for medicines; nevertheless, it is necessary to have other additional criteria that contrast with the results related to the quantity of expired medicine because otherwise, the best results will be to accept only medicines with expiration dates of 12 months or more. Thus, before balancing inventory levels, the models presented should consider the demand and the expiration dates. Therefore, in cases where the expiration dates are short compared to the planning horizon, the inventory tends to be zero because all the medicines that are not used to satisfy the demand are lost.

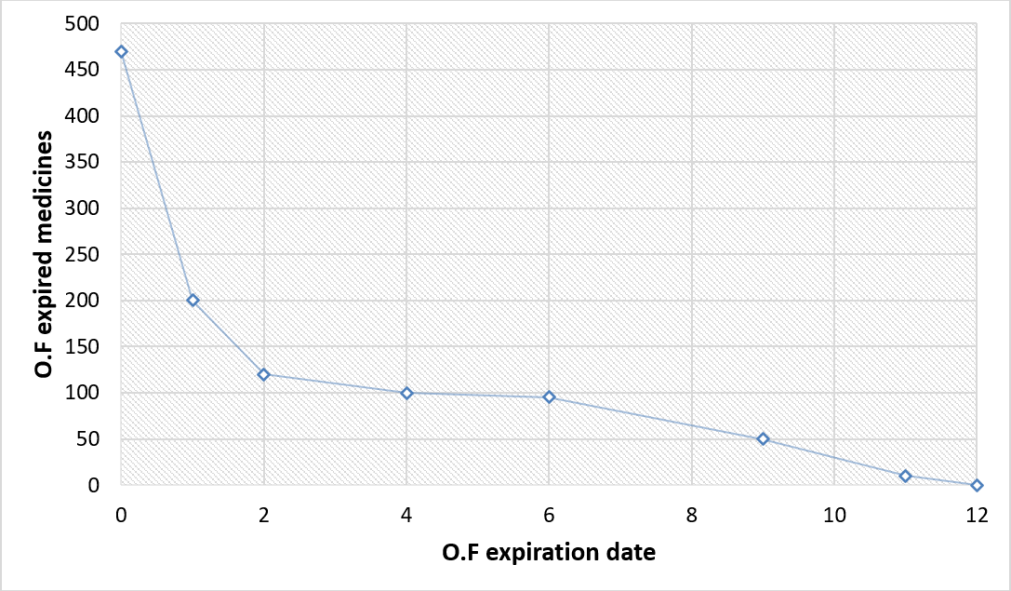

Figure 4.6: Pareto frontier O.F 1 versus O.F 2

The comparison between the levels of expired medicines and inventory levels are presented in Figure 4.7.

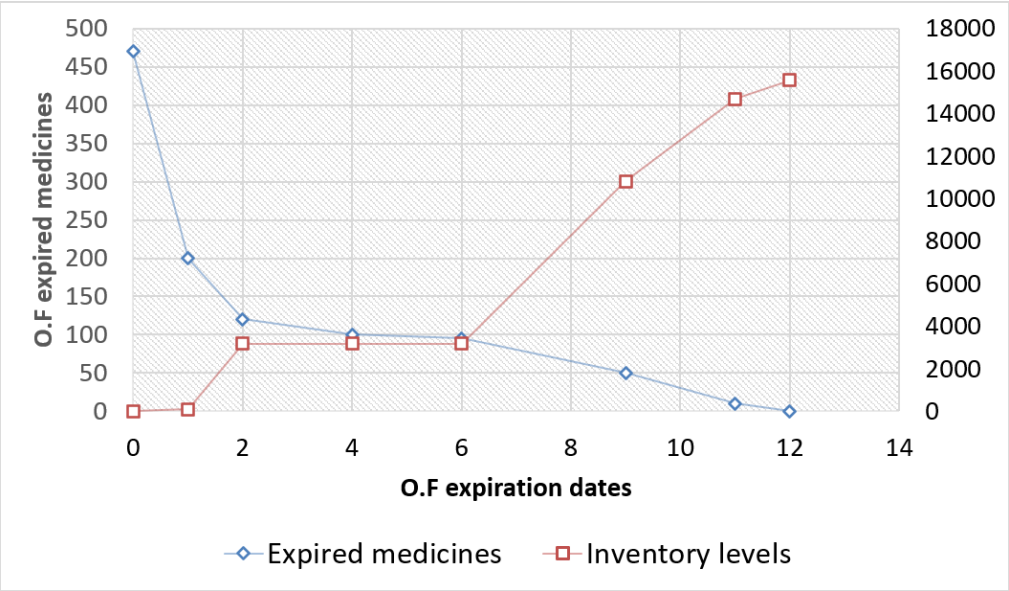

Figure 4.7: Contrast of pareto frontier versus inventory levels

The blue curve represents the expired medicine, for which the scale of units is on the left-hand side of the figure. The orange curve represents the inventory levels, for which the scale of units is on the right-hand side of the figure. It can be observed that while the quantity of expired medicine decreases through the increments of the expiration dates, the inventory levels increase. Considering the behavior of these two variables, it is a fact that there are some points where the lines change their behavior; for inventory levels, there are always increasing values, and for expired medicine, there are decreasing values. Even the scales showing the results of these two variables are different. It can be observed that in 6 months, there is a point at which the two graphs converge, presenting a breakpoint where they change their behavior. Even though the final decision depends on the decision makers, based on the results of this model, an acceptable decision that generates a balance between expired medicines and inventory levels is to accept medicines with expiration dates of at least 6 months: with this decision, less than 100 units of expired medicines are obtained and the inventory levels are not greater than 2000 units.

4.7 Conclusions

This chapter proposes the use of a simulation-optimization approach based on the stochastic counterpart or sample path method for solving pharmaceutical logistics

problems under uncertainty in hospitals. Based on this approach, two mathematical models based on a real case considering different sources of uncertainty and other elements related with legal regulations have been proposed. The first model determines the amount of medicines that must be purchased from a specific supplier in a specific time period, considering constraints of age based inventory, human resource capacities and service level. The model aims to minimize the overall costs of managing medicines in hospitals, considering that the the demand, lead times and cost of medicines are random. The second model determines an acceptable expiration date of medicines in order to minimize the amount of expired medicines.

The results of the mathematical model have been evaluated over real data and simulated scenarios. The solution obtained by the model was compared with the policy used by the hospital under similar conditions (taking into account the real data of hospital). The results show that in most of the cases (17 of 22 medicines), the results of the supply and managing of medicines were improved, and if the policy obtained by the model proposed were implemented, considering the 22 medicines, it would be possible to reduce the total costs of the managing of medicines by 15.86%. The optimal policy evaluated on both real and simulated data shows better performances for three indicators (inventory levels, total of the expired medicines and emergency purchases) than the hospital policy.

These models can help to define policies for negotiation with medicine suppliers in terms of the medicines' expiration dates, emergency purchases prices and lead times, thereby enabling more cost savings. Future work will include the development of algorithms to allow the inclusion of larger scale of type of medicines and other approaches to model the uncertainties. Finally, the study of high costs of medicines is also necessary in order to improve supply chain management.

Chapter 5

Resilent network design under uncertainty in a location-allocation of hospital pharmacy robots

Contents

This chapter presents two mathematical models to optimize the process related to unit-doses and prescriptions management and distribution in a network of hospitals where also a location-allocation of pharmacy robots decisions are evaluated. The first one a deterministic model that considers the real operational constraints of the process of preparing and distributing unit-doses (WHO requirement) and prescriptions. The second one a stochastic model in which the uncertainty of demand of medicines and the multi-source resilience strategy are considered. The uncertainty of the demand of medicine is included by using the p-robustness approach that combines the minimization of the expected cost and the minimization of the worst case or regret. The multi-source resilience strategy is considered to avoid the risk of centralized distribution processes in a very sensitive network managing the demand of medicines and prescriptions.

5.1 Introduction

Access to medicines and reliability in the pharmaceutical requirements of patients is one of the most important challenge in primary healthcare. To deal with this, automation technologies have become a support in the pharmaceutical services that helps hospitals to minimize human errors, minimize costs and improve efficiency of processes. In this way, the term pharmacy automation appears as the process of automating the routine tasks performed in pharmacies [Ahadani 2012] [Altawalbeh 2018]. The related work within pharmacies consists in storing medicines, making unit-doses, preparing prescriptions and delivering prescriptions to patients. Critical errors may occur during the two last steps. Automatic dispensing systems is an innovative tool that allows hospitals not only to satisfy requirements of patients but also optimize the distribution of medicines across a network of interconnected facilities [Spinks 2017].

In this context the main purpose of this chapter is to develop mathematical models to determine the location of different types of robots (cutting storage preparing unit doses and prescriptions) in a network of hospitals and the allocation of hospitals for satisfy the requirements of patients considering uncertainty in demand and a multi-source resilience strategy.

5.2 Background

Location-allocation problems solution approaches and applications have been widely studied in the scientific literature [Murat 2011], [Karatas 2018] and [Ortiz-Astorquiza 2017]. An application of location and reorganization in health systems is developed in [Guerriero 2016]. This paper presents a real application in a healthcare system in Italy. Two problems are considered: (i) healthcare reorganization problem considering regional guidelines that aim to replace some ordinary admissions by ambulatory or home cares and (ii) build a new model that considers the demand satisfaction and the increasing of the hospital capacity. A similar work is proposed in [Shariff 2012].

A location-allocation model under uncertainty for hospital network planning is proposed in [Mestre 2014]. The total cost of the network of hospitals is minimized as the expected distance to facilities. The authors developed a two-stage model: the first stage is limited to decisions related to location and the second stage involves location and allocation decisions. This model is applied to a real case in Portugal with two types of hospitals: non-specialized hospitals close to the population and high specialized ones that could stand far from the demand.

A similar two-stage approach is developed in [Karamyar 2016]. The main idea is to determine the hospital location, then the allocation of services and machines and finally assign patients to services. The authors proposed a bi-objective robust model

assuming that costs are uncertain. Other multi-objective models are applied to the location and sizing of medical departments in a hospital network in [Zhang 2016] and [Stummer 2004]. A similar problem is studied in [Coskun 2010] for emergency medical service stations.

A robust approximation for a multi-period location-allocation problem of pharmaceutical centers is proposed in [Haji abbas 2016]. A multi-objective model is used by considering the minimization of costs and the maximization of customer's satisfaction. Epsilon constraint approach is used for solving the bi-objective model. The robustness is considered regarding the uncertainty in demand.

A healthcare application applied to emergency response in case of disaster is developed in [Pietz 2009]. A hybrid model is presented combining a simulation model and a nonlinear optimization model of the assignment of workers to workstations which is solved by simulation and a heuristic optimization algorithm. Decisions are related to the locations for dispensing aids and the design of the logistics to supply the demand. A review for location problems in emergencies is presented in [Boonmee 2017].

In [Bowers 2015] is proposed a model to locate services in a musculoskeletal physiotherapy department in which the patient behavior is modeled using heuristics such as preferences of locations of services and heterogeneity of patients. The model considers the individuality of patients along with the availability of resources. It uses simulation where scenarios correspond to different configurations of services. Several applications of facility location and extension are presented in these two surveys [Ahmadi-Javid 2017], [Güne 2015]. [Chauhan 2016] present an application of location for waste material in healthcare.

There are some recent developments in location problems. A combined problem of location and routing problem is defined in [Nedjati 2017] and solved with a genetic algorithm. Approximate dynamic programming is used for solving a stochastic location problem in [Meissner 2018], the problem consists in determine the optimal policy that indicates the sources and destinations of transhipment under stochastic demand. Other applications for different variants of location-allocation problems can be found in [Gokbayrak 2017], [Mogale 2018], [Saghiri 2018] and [Ghaffarinasab 2018].

5.3 Methods

In this chapter the problem addressed correspond to location-allocation of pharmaceutical robots (strategic) that prepares prescriptions and unit-doses to be distributed over a network of hospitals, once the problem of location-allocation is solved, the second problem consists in determine the distribution network (operational), in order to distribute medicines (unit-doses and/or prescriptions) for those

hospitals who can't produce it.

The methodology used to address this problem consist in the development of two mathematical models: (i) a deterministic model and (ii) stochastic p-robustness model. For the deterministic mathematical model, the operational constraints related to preparation and distribution of unit-doses and prescriptions were built based on the requirements and guidelines of the network of hospitals. Based on the first model, a stochastic model is proposed considering (i) the variability of the demand using a p-robustness level and generating scenarios of demand of medicines. The scenarios are built based on the information provided by the network of hospitals in relation of how is expected to increase/decrease the demand (+-30% in the planning horizon of 7 years) and (ii) the multi-source resilience strategy to avoid the risk of centralized distribution process in a very high and sensitive distribution network. The methodology used in this work is presented in Figure 5.1.

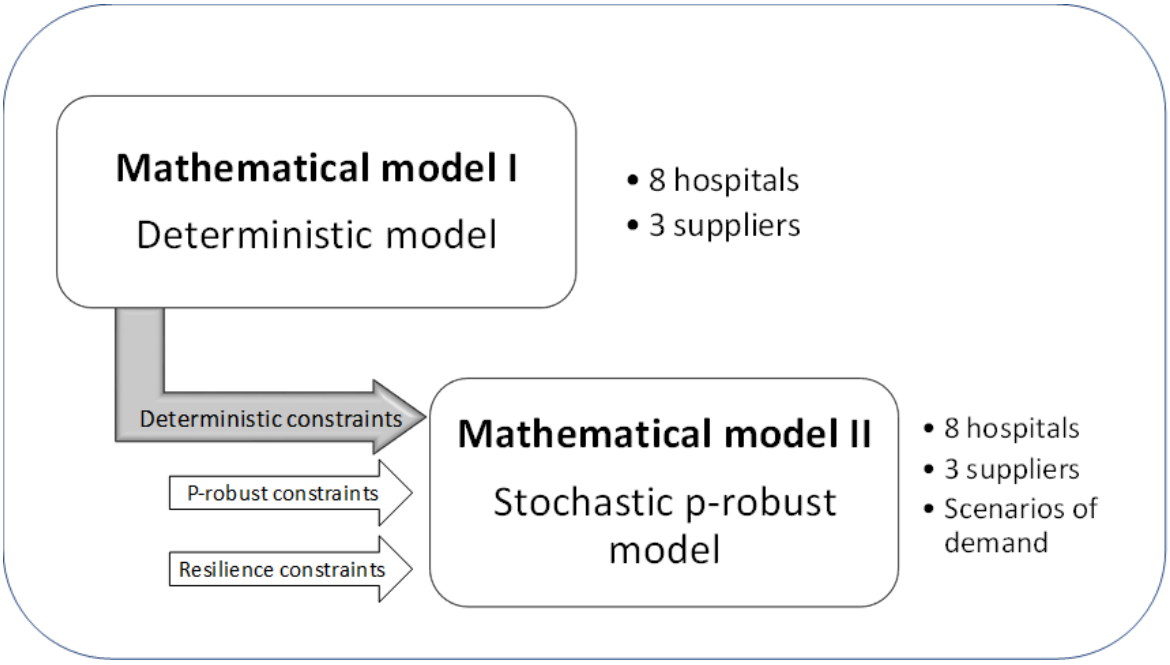

Figure 5.1: Methodology

P-Robustness method

The main idea of the p-robust optimization method is to combine the benefits of stochastic optimization and robust optimization by minimizing the expected cost and min-max cost or regret by looking for the maximal expected profit solution that can be defined as p-robust [Mazidi 2019], [Snyder 2006]. Any problem can be defined as p-robust if it satisfied the following constraint (5.1) :

$$\frac{Z_s^* - Z_s(X)}{Z_s^*} \leq p \tag{5.1}$$

Where Z_s^* is the optimal objective function for each scenario s $\in S, Z_s(X)$ the objective function of a feasible vector X under scenario s and p the desired p-robustness level. The left part of the equation is the relative regret.

5.4 Mathematical models

5.4.1 Problem description

The optimization problems considered in this chapter are modeled as an extension of a location-allocation considering distribution of unit-doses and prescriptions decisions. The objective function consists in determining the best location and allocation of different types of pharmaceutical robots for a network of hospitals minimizing the total costs over the planning horizon. Three types of robots are considered: (i) robots that process medicines from suppliers and produce unit-doses (i.e. medicines are extracted from their boxes and cut into unit-doses) named cutting robots; (ii) storage robots that store unit-doses, and (iii) prescription robots that process unit-doses to compose personalized prescriptions depending on patient requirements (i.e. unit-doses of different medicines are grouped together in a plastic bag to compose a prescription) . Storage and prescription robots can be bought with different settings, i.e. different costs and capacities. Each hospital of the network can have robots of each type. The general process to satisfy the demand of prescriptions is presented in Figure 5.2.

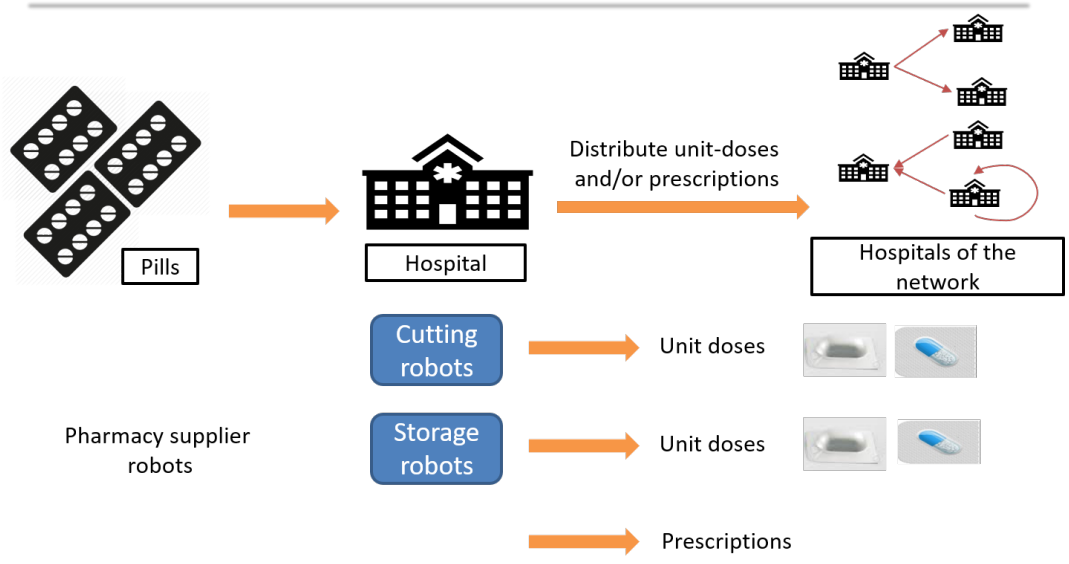

Figure 5.2: Description of the general process of preparing prescriptions

Hospitals treat patients and in some cases pharmacies allocate robots for preparing prescriptions. When a requirement of medicines is identified the demand of patient is converted into a recipe of medicines required to the personnel in charge of preparing these recipes. In parallel this area cut the medicines to prepare unit-doses to distribute to patients. When a requirement of specific medicines is made, the robot that prepares prescriptions collect a number of unit-doses in the storage area and put into a single package to be distributed.

Figure 5.3 shows an illustrative example of this process, considering a network of three hospitals H1, H2 and H3, dotted line arrows represent unit-doses flows whereas hard line arrows represent prescription flows. The network design is: H1 has one cutting robot producing unit-doses (R1), one prescription robot (R2) and one storage robot (R4); H2 has one prescription robot (R3) and one storage robot (R5); H3 has no robots. The distribution plan is: H1's robot R1 produces unit-doses for H1 (stored in R4) and H2 (stored in R5); H1's robot R2 produces prescriptions for H1 only. Unit-doses are distributed from H1 to H2. H2's robot R3 produces prescriptions using unit-doses received from H1 for H2 and H3. Prescriptions are distributed from H2 to H3.

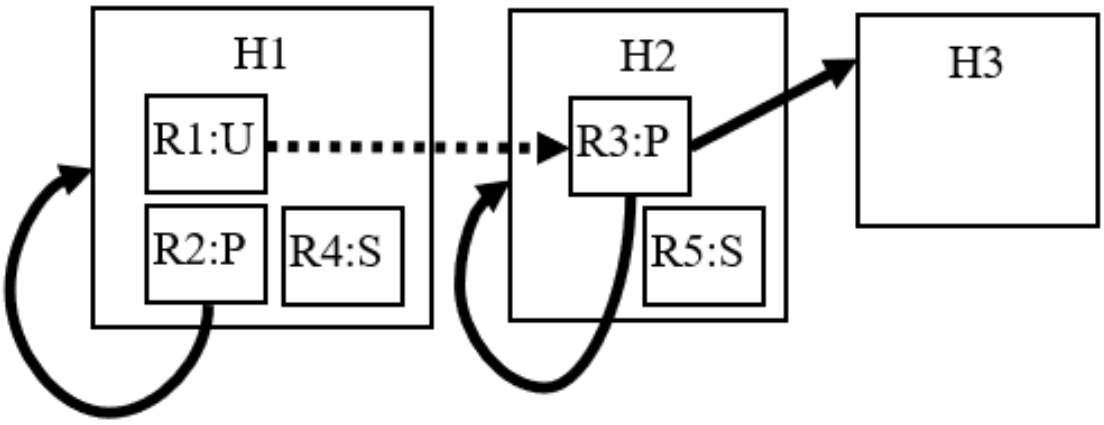

Figure 5.3: Illustrative example of a configuration of network design

In this problem two types of decisions are considered: (i) the number of robots of each type to locate in each hospital, and (ii) the distribution flow over the network (i.e. which hospitals provide unit-doses and/or prescriptions for which hospital). Based on this two mathematical models are proposed. In the first one the demand for medicines for each hospital is deterministic whereas in the second model this demand is stochastic.

5.4.2 Assumptions

The proposed mathematical models were built considering the information provided by the manager of the hospital and the chief of the pharmacy area by using their own estimations and guidelines.

The following are the assumptions considered in this approach for both mathematical models:

- Assumption A1: In the deterministic model the demand is assumed to be constant over the planning horizon
- Assumption A2: Decisions are strategic based on an investment horizon of 7 years
- Assumption A3: The utilization rate of robots is fixed to 70% assuming some interruptions and maintenance
- Assumption A4: There aren't considerations about network disruptions (ie:failures of robots, road breaks..)
- Assumption A5: The processing times of robots are assumed to be constant
- Assumption A6: The different costs are assumed to be constant over the planning horizon considered
- Assumption A7: The daily and annual opening times of hospitals are assumed to be constant over the planing horizon

5.4.3 Deterministic model

The deterministic mathematical model is formulated by the following elements:

Sets

i	Set of hospitals, $i \in H = \{1,2,...,H\}$
pm	Set of configurations of prescription robots, $pm \in PM = \{1,2,...,PM\}$
sm	Set of configurations of storage robots, $sm \in SM = \{1,2,...,SM\}$

Parameters

UR	Utilization rate of robots
TCU_{ij}	Distribution costs of unit-doses between hospitals
TCP_{ij}	Distribution costs of prescriptions between hospitals

OP_i	Annual opening hours per hospital
D_i	Requirements of unit-doses per year in each hospital
PU	Price of unit-doses (cutting)
DH_i	Number of daily working hours per hospital
$CapPP_{pm}$	Capacities of preparing prescriptions per configuration
$CostPP_{pm}$	Cost of prescription robots for each configuration
Am	Years of investment
UDP_i	Number of unit-doses per prescription in each hospital
$CapS_{sm}$	Storage capacity of each configuration
$CostS_{sm}$	Cost of storage robots for each configuration
$CostC$	Unitary cost of cutting robots
$CapProd$	Capacity of cutting robots
M	Big number

Variables

A_{ij}	Number of unit-doses distributed each year between hospitals i and j
B_{ij}	Number of prescriptions distributed each year between hospitals i and j
N_i	Number of cutting robots in each hospital
DM_{pmi}	Number of prescriptions robots per configuration in each hospital
SM_{smi}	Number of storage robots per configuration in each hospital
x_{ij}	$\begin{cases} 1 \text{ if there is distribution of unit-doses between hospitals i and j} \\ 0 \text{ otherwise} \end{cases}$
y_{ij}	$\begin{cases} 1 \text{ if there is distribution of prescriptions between hospitals i and j} \\ 0 \text{ otherwise} \end{cases}$
	In this case x_{ij} and y_{ij} are the variables related with the allocation of hospitals

Objective

The objective function minimizes the overall costs composed by (i) cutting costs, (ii) distribution costs and (iii) investment costs. Cutting costs represents the cost of producing unit-doses. Distribution cost is composed by costs of distribution of unit-doses and costs of distribution of prescriptions. The investment cost is composed by costs of prescription/storage robots and cost of unit-doses robots. This objective function is defined by the following equation:

$$Min\ z = PU * Am * \sum_{i \in H} \sum_{j \in H} A_{ij} + \sum_{i \in H} \sum_{j \in H} (TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm \in PM} \sum_{i \in H} CostPP_{pm} * DM_{pmi} + \sum_{sm \in SM} \sum_{i \in H} CostS_{sm} * SM_{smi} + \sum_{i \in H} CostC * N_i$$

Constraints

1. The cutting robots are enough to satisfy the distribution of unit-doses between hospitals.

$$N_i * CapProd * OP_i * UR \geq \sum_{k \in H} A_{ik} \qquad \forall i \in H$$

2. The robots for preparing prescriptions in each hospital are enough to satisfy the prescriptions distributed between hospitals (the capacity of prescriptions for each type of robot is expressed in terms of unit-doses).

$$\sum_{pm \in PM} CapPP_{pm} * DM_{pmi} * OP_i * UR \geq \sum_{k \in H} B_{ik} * UDP_k \qquad \forall i \in H$$

3. Storage capacity. Each hospital must guarantee at least five days of distribution of unit-doses. Prescriptions contain a certain number of unit-doses.

$$\sum_{sm \in SM} CapS_{sm} * SM_{smi} \geq \sum_{j \in H} A_{ij} * (\frac{5}{365}) \qquad \forall i \in H$$

4. Balancing the number of unit-doses received and the number of unit-doses dispatched in terms of prescriptions for each hospital.

$$\sum_{j \in H} A_{ji} = \sum_{j \in H} B_{ji} * UDP_j \qquad \forall i \in H$$

5. For each hospital there must be at most the same number of prescription robots and storage robots because the storage robots are join to the prescription robots.

$$\sum_{pm \in PM} DM_{pmi} \leq \sum_{sm \in SM} SM_{smi} \qquad \forall i \in H$$

6. The satisfaction of demand in terms of unit-doses.

$$\sum_{i \in H} UDP_j * B_{ij} \geq D_j \qquad \forall j \in H$$

7. Relationship between the binary variables of distribution of unit-doses and prescriptions with the integer variables of distribution of unit-doses and prescriptions.

$$A_{ij} \leq M * x_{ij} \qquad \forall i, j \in H$$

$$B_{ij} \leq M * y_{ij} \qquad \forall i, j \in H$$

8. Distribution of unit-doses is not allowed in two directions, this means that a hospital can supply other hospital, but the supplied hospital cannot supply in return the previous one.

$$x_{ji} \leq 1 - x_{ij} \qquad \forall i, j \in H | i <> j$$

9. For medicines flow requirements, each hospital can only receive unit-doses from only one hospital.

$$\sum_{i \in H} x_{ij} \leq 1 \qquad \forall j \in H$$

10. Each hospital can only receive prescriptions for at most one hospital or by itself.

$$\sum_{i \in H | i <> j} y_{ij} \leq 1 \qquad \forall j \in H$$

11. The capacity of cutting robots in terms of unit-doses is enough for the daily demand of unit-doses.

$$CapProd * N_i * DH_i * UR \geq \frac{1}{365} * \sum_{j \in H} A_{ij} \qquad \forall i \in H$$

12. Each hospital only can satisfy its own demand if prescription robots are located there.

$$\sum_{i \in H | i=j} y_{ij} \leq \sum_{pm \in PM} M * DM_{pmj} \qquad \forall j \in H$$

13. Distribution of unit-doses can only be made by hospitals that locate cutting robots in their own hospitals.

$$CapProd * N_i \geq \sum_{j \in H} A_{ij} \qquad \forall i \in H$$

14. Distribution of prescriptions can only be made by hospitals in which prescription robots are located.

$$\sum_{pm \in PM} DM_{pmi} \geq \sum_{j \in H} B_{ij} \qquad \forall i \in H$$

15. For each hospital that distribute prescriptions there are enough daily capacity to ensure at least 4 days of making prescriptions.

$$\sum_{pm \in PM} CapPP_pm * DM_{pmi} * DH_i * UR \geq \sum_{j \in H} B_{ij} * \frac{4}{365} \qquad \forall i \in H$$

16. The domain definition of variables.

$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \geq 0; \qquad x_{ij}, y_{ij} \in \{0, 1\}$$
$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \in \mathbb{Z}$$

The deterministic model for location of pharmaceutical robots, allocation of hospitals and distribution of unit-doses and prescriptions is summarized as follows:

$$Min\ z = PU * Am * \sum_{i\in H}\sum_{j\in H} A_{ij} + \sum_{i\in H}\sum_{j\in H}(TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm\in PM}\sum_{i\in H} CostPP_{pm} * DM_{pmi} + \sum_{sm\in SM}\sum_{i\in H} CostS_{sm} * SM_{smi} + \sum_{i\in H} CostC * N_i \quad (5.2)$$

Subject to:

$$N_i * CapProd * OP_i * UR \geq \sum_{k\in H} A_{ik} \qquad \forall i \in H \quad (5.3)$$

$$\sum_{pm\in PM} CapPP_{pm} * DM_{pmi} * OP_i * UR \geq \sum_{k\in H} B_{ik} * UDP_k \qquad \forall i \in H \quad (5.4)$$

$$\sum_{sm\in SM} CapS_{sm} * SM_{smi} \geq \sum_{j\in H} A_{ij} * (\frac{5}{365}) \qquad \forall i \in H \quad (5.5)$$

$$\sum_{j\in H} A_{ji} = \sum_{j\in H} B_{ji} * UDP_j \qquad \forall i \in H \quad (5.6)$$

$$\sum_{pm\in PM} DM_{pmi} \leq \sum_{sm\in SM} SM_{smi} \qquad \forall i \in H \quad (5.7)$$

$$\sum_{i\in H} UDP_j * B_{ij} \geq D_j \qquad \forall j \in H \quad (5.8)$$

$$A_{ij} \leq M * x_{ij} \qquad \forall i, j \in H \quad (5.9)$$

$$B_{ij} \leq M * y_{ij} \qquad \forall i, j \in H \quad (5.10)$$

$$x_{ji} \leq 1 - x_{ij} \qquad \forall i, j \in H | i <> j \quad (5.11)$$

$$\sum_{i\in H} x_{ij} \leq 1 \qquad \forall j \in H \quad (5.12)$$

$$\sum_{i\in H | i<>j} y_{ij} \leq 1 \qquad \forall j \in H \quad (5.13)$$

$$CapProd * N_i * DH_i * UR \geq \frac{1}{365} * \sum_{j \in H} A_{ij} \qquad \forall i \in H \tag{5.14}$$

$$\sum_{i \in H | i=j} y_{ij} \leq \sum_{pm \in PM} M * DM_{pmj} \qquad \forall j \in H \tag{5.15}$$

$$CapProd * N_i \geq \sum_{j \in H} A_{ij} \qquad \forall i \in H \tag{5.16}$$

$$\sum_{pm \in PM} DM_{pmi} \geq \sum_{j \in H} B_{ij} \qquad \forall i \in H \tag{5.17}$$

$$\sum_{pm \in PM} CapPP_pm * DM_{pmi} * DH_i * UR \geq \sum_{j \in H} B_{ij} * \frac{4}{365} \qquad \forall i \in H \tag{5.18}$$

$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \geq 0; \qquad x_{ij}, y_{ij} \in \{0,1\}$$
$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \in \mathbb{Z} \tag{5.19}$$

5.4.4 Stochastic model

According to Sheffi [Sheffi 2005], Nemeth [Nemeth 2008] and Mensah[Mensah 2014] resilience in supply chains is defined as the ability of organizations to bounce back from large scale disruptions such as random events, accidents, negligence, intentional disruptions, natural disasters or or technological threats (e g equipment breakdown).

One of the most common resilience strategy referenced in the literature to reduce the risk of disruption is the multiple sourcing [Namdar 2017].This strategy has been adopted in the stochastic model by adding additional constraints in order to avoid centralized solutions increasing the flexibility in the distribution of medicines. An example of this resilience strategy is shown in figure 5.4, where two different types of configurations can be observed, the first one a very centralized configuration in which the location of robots is over a single hospital and in the second one the configuration of the network is split over three hospitals allowing to react in case of a disruption over the network. In this figure the triangles represent the hospitals in the network while dotted lines represents the distribution of unit-doses and lines represents the distribution of prescriptions. Each hospital where are located robots can satisfy its own demand and the demand of hospitals assigned.

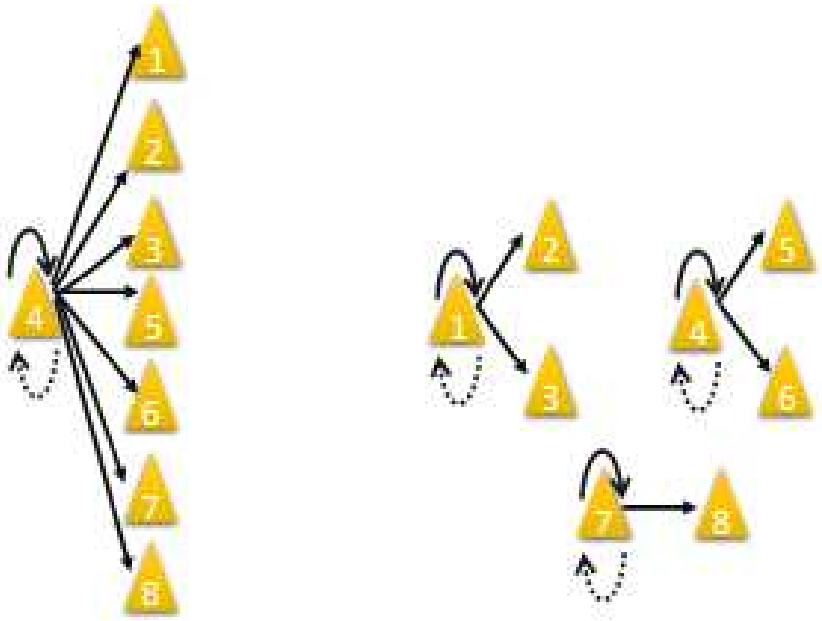

Figure 5.4: Concept of resilience strategy used in this work

Since decisions of purchasing robots are made on a strategic level, the uncertainty in demand is considered as a factor of analysis. The concept of p-robustness presented in section 5.3 has been added and modified by including in the objective function the new terms related to the uncertainty and including the scenarios of the demand and the p-robust constraint ensuring a p-robust desire level. The new terms added to the mathematical model presented in subsection 5.4.3 and based on the concept of p-robustness [Snyder 2006] and non-scenario dependent modeling [Mestre 2014] is as follows:

Sets

Additionally to the sets used in the deterministic model (section 5.4.3), the stochastic model use the following sets:

scn	Set of scenarios of variation of demand $sm \in SM = \{1,2,...,\text{SCN}\}$

Parameters

Additionally to the parameters used in the deterministic model (section 5.4.3), the stochastic model use the following parameters:

p	Desired robustness level

D_{scn}	Requirements of unit-doses by hospital in each scenario
q_{scn}	Probability that a scenario occurs
z^*_{scn}	Optimal objective value of the location-allocation of robots for scenario *scn*

Variables

The variables used in the stochastic model are the same of the deterministic model (section 5.4.3).

Objective

The new objective function minimizes the expected distribution cost and the cost of location of robots overall scenarios.

$$Min\ z = \sum_{scn \in SCN} q_{scn}[\sum_{i \in H}\sum_{j \in H} PU * Am * A_{ij} + \sum_{i \in H}\sum_{j \in H}(TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm \in PM}\sum_{i \in H} CostPP_{pm} * DM_{pmi} + \sum_{sm \in SM}\sum_{i \in H} CostS_{sm} * SM_{smi} + \sum_{i \in H} CostC * N_i]$$

Constraints

1. Constraints 5.24 to 5.42 are similar to equations 5.3 to 5.19 of the discrete model except for variables having the index of scenarios of demand:

$$\sum_{i \in H} UDP_j * B_{ij} \geq D_{scn} \qquad \forall j \in H, \forall scn \in SCN$$

2. The p-robustness condition that is a measure that combines the minimization of the expected costs and the minimization of the worst-case cost or relative regret. It is mandatory to compute the optimal solution for each scenario to use the concept of p-robustness.

$$\sum_{i \in H}\sum_{j \in H} PU * Am * A_{ij} + \sum_{i \in H}\sum_{j \in H}(TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm \in PM}\sum_{i \in H} CostPP_{pm} * DM_{pmi} + \sum_{sm \in SM}\sum_{i \in H} CostS_{sm} * SM_{smi} + \sum_{i \in H} CostC * N_i \leq (1 + p) * z^*_{scn}$$

3. The multi-source resilience strategy is modeled by adding constraints to the model that guarantees to have at least two hospitals where robots are located.

$$\sum_{pm \in PM} DM_{pmi} \geq 1 \qquad \forall i \in H | i = \text{bigger hospitals}$$

The stochastic mathematical model for location of pharmaceutical robots, allocation of hospitals and distribution of unit-doses and prescriptions considering uncertainty of demand of medicines and resilience is summarized as follows:

$$Min\ z = \sum_{scn \in SCN} q_{scn}[\sum_{i \in H}\sum_{j \in H} PU * Am * A_{ij} + \sum_{i \in H}\sum_{j \in H}(TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm \in PM}\sum_{i \in H} CostPP_{pm} * DM_{pmi} + \sum_{sm \in SM}\sum_{i \in H} CostS_{sm} * SM_{smi} + \sum_{i \in H} CostC * N_i] \quad (5.20)$$

Subject to:

$$\sum_{i \in H}\sum_{j \in H} PU * Am * A_{ij} + \sum_{i \in H}\sum_{j \in H}(TCU_{ij} * Am * x_{ij} + y_{ij} * Am * 2 * TCPij) + \sum_{pm \in PM}\sum_{i \in H} CostPP_{pm} * DM_{pmi} + \sum_{sm \in SM}\sum_{i \in H} CostS_{sm} * SM_{smi} + \sum_{i \in H} CostC * N_i \leq (1+p) * z^*_{scn} \quad (5.21)$$

$$\sum_{i \in H} UDP_j * B_{ij} \geq D_{scj} \qquad \forall j \in H, \forall sc \in SC \quad (5.22)$$

$$\sum_{pm \in PM} DM_{pmi} \geq 1 \qquad \forall i \in H | i = \text{biggest hospitals} \quad (5.23)$$

$$N_i * CapProd * OP_i * UR \geq \sum_{k \in H} A_{ik} \qquad \forall i \in H \quad (5.24)$$

$$\sum_{pm \in PM} CapPP_{pm} * DM_{pmi} * OP_i * UR \geq \sum_{k \in H} B_{ik} * UDP_k \qquad \forall i \in H \quad (5.25)$$

$$\sum_{sm \in SM} CapS_{sm} * SM_{smi} \geq \sum_{j \in H} A_{ij} * (\frac{5}{365}) \qquad \forall i \in H \quad (5.26)$$

$$\sum_{j \in H} A_{ji} = \sum_{j \in H} B_{ji} * UDP_j \qquad \forall i \in H \quad (5.27)$$

$$\sum_{pm \in PM} DM_{pmi} \leq \sum_{sm \in SM} SM_{smi} \qquad \forall i \in H \tag{5.28}$$

$$\sum_{j \in H} A_{ji} = \sum_{j \in H} B_{ji} * UDP_j \qquad \forall i \in H \tag{5.29}$$

$$\sum_{pm \in PM} DM_{pmi} \leq \sum_{sm \in SM} SM_{smi} \qquad \forall i \in H \tag{5.30}$$

$$\sum_{i \in H} UDP_j * B_{ij} \geq D_j \qquad \forall j \in H \tag{5.31}$$

$$A_{ij} \leq M * x_{ij} \qquad \forall i, j \in H \tag{5.32}$$

$$B_{ij} \leq M * y_{ij} \qquad \forall i, j \in H \tag{5.33}$$

$$x_{ji} \leq 1 - x_{ij} \qquad \forall i, j \in H | i <> j \tag{5.34}$$

$$\sum_{i \in H} x_{ij} \leq 1 \qquad \forall j \in H \tag{5.35}$$

$$\sum_{i \in H | i <> j} y_{ij} \leq 1 \qquad \forall j \in H \tag{5.36}$$

$$CapProd * N_i * DH_i * UR \geq \frac{1}{365} * \sum_{j \in H} A_{ij} \qquad \forall i \in H \tag{5.37}$$

$$\sum_{i \in H | i = j} y_{ij} \leq \sum_{pm \in PM} M * DM_{pmj} \qquad \forall j \in H \tag{5.38}$$

$$CapProd * N_i \geq \sum_{j \in H} A_{ij} \qquad \forall i \in H \tag{5.39}$$

$$\sum_{pm \in PM} DM_{pmi} \geq \sum_{j \in H} B_{ij} \qquad \forall i \in H \tag{5.40}$$

$$\sum_{pm \in PM} CapPP_pm * DM_{pmi} * DH_i * UR \geq \sum_{j \in H} B_{ij} * \frac{4}{365} \qquad \forall i \in H \tag{5.41}$$

$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \geq 0; \qquad x_{ij}, y_{ij} \in \{0, 1\}$$
$$A_{ij}, B_{ij}, N_h, DM_{pmi}, SM_{smi} \in \mathbb{Z} \tag{5.42}$$

5.5 Experimental settings

5.5.1 Problem instance description

A real case study related to the "Rhone Nord Beaujolais Dombes" territorial hospital network is proposed to illustrate the results of the mathematical model and its applicability in a realistic case. The network located in the north of Lyon (France) has 8 different hospitals spread in the region, and each one has different consumptions and treat different types of illnesses; they have different levels of demand. Results are analyzed considering key performance indicators (costs of the provided solutions) and qualitative indicators (network design).

The case study analyzed in this work consider a network of hospitals with the following characteristics:

- 8 hospitals in the network
- Overture times (annual) varies between 1,690 (Scenario 1) and 2,820 (Scenario 2) hours per year
- The number of prescriptions varies between 387,581 and 3,038,490 per year
- 3 types of suppliers of robots, each one with different types of robots, configurations and capacities
- The suppliers has one configuration of robots for each type of process (prescription preparation and storage of unit-doses)
- Daily opening hours varies between 6.5h to 8.5h
- Capacities of robots can be increased

5.5.2 Deterministic model results

The total costs obtained by the deterministic model 5.4.3 are presented in Tables 5.1 and 5.2 which corresponds to the two different scenarios: minimum value and maximum value of 1690 and 2820 opening hours respectively. The costs have been normalized for confidential reasons.

		Costs			
		Total costs	Preparing unit doses	Distribution	Investments
Scenario 1,1690 hours	Supplier 1	1.00	1.00	1.00	0.76
	Supplier 2	0.38	0.10	0.94	1.00
	Supplier 3	0.55	0.39	0.84	0.83

Table 5.1: Deterministic model costs of scenario 1

		Costs			
		Total costs	Preparing unit doses	Distribution	Investments
Scenario 2,2820 hours	Supplier 1	1.00	1.00	1.00	0.79
	Supplier 2	0.38	0.10	0.88	1.00
	Supplier 3	0.55	0.39	0.89	0.83

Table 5.2: Deterministic model costs of scenario 2

Results are presented with the total cost classified into unit doses costs (preparing unit doses), distribution costs (of prescriptions and unit doses) and investment costs. In both cases the best result is obtained by supplier 2 due principally to lower unit doses costs. The lower costs in both scenarios corresponds to the distribution costs that in the higher case corresponds to 6.04% of the total cost.

Tables 5.3 and 5.4 present the detailed solution of location of robots for both scenarios, it contains for each supplier the number and the location of the robots in the network of hospitals. Each supplier has different types of robots for each process, in the solution robots are presented as T1, T2, ..., and so on depending on the configuration and the supplier. For example in Table 5.3 for the supplier 2 the hospitals H2, H3 and H1 are considered for locating the robots T1 (1, 0 and 4 units respectively) and robots T2 (2, 1 and 3 units respectively).

Figures 5.5 and 5.6 present the detailed solution of the allocation of hospitals (configuration of the network), the dotted line represents the preparation of unit-doses and the continuous line represents the distribution of prescriptions (allocation). For example in figure 5.5, for the supplier 2, hospitals H2, H3 and H1 prepares unit-doses and hospital H2 distribute prescriptions to hospitals H6 and H8, hospital H1 distribute prescriptions to hospitals H7, H4 and H5. Additionally, in hospitals where robots are located it must be enough capacity to satisfy their own demand of prescriptions, in this case for hospitals H2, H3 and H1.

Supplier 1		Supplier 2				Supplier 3		
Robots	H1	Robots	H2	H3	H1	Robots	H4	H1
T1	5	T1	1	0	4	T1	1	6
T2	3	T2	2	1	3	T2	1	0
T3	3					T3	0	1
						T4	1	0

Table 5.3: Deterministic model solution for location of robots scenario 1

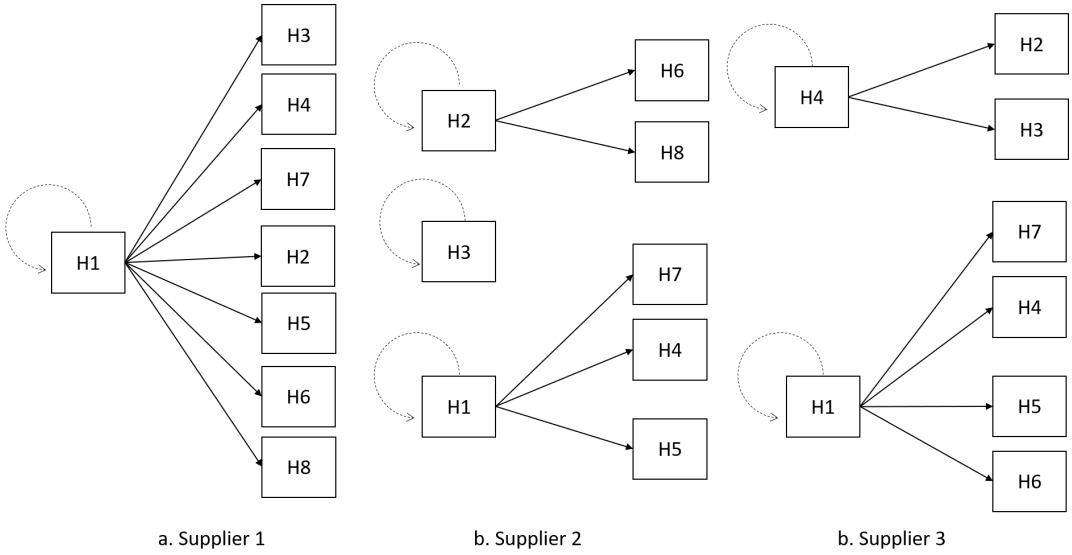

Figure 5.5: Configuration of the network for scenario 1

Supplier 1			Supplier 2				Supplier 3		
Robots	H2	H1	Robots	H2	H4	H1	Robots	H2	H1
T1	2	3	T1	2	1	2	T1	2	6
T2	1	2	T3	4	2	5	T2	1	0
T3	1	2					T3	0	1

Table 5.4: Deterministic model solution for location of robots scenario 2

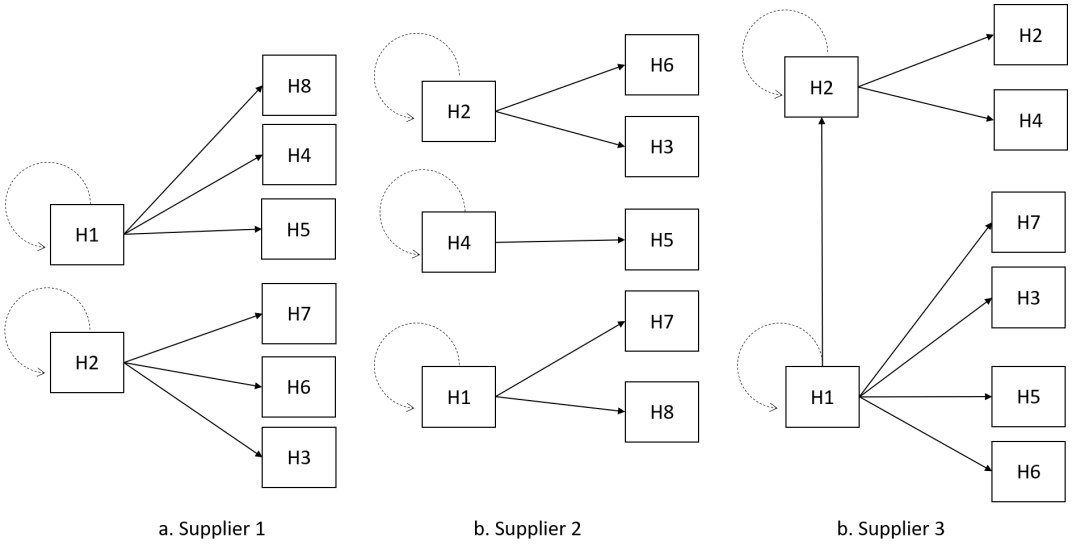

Figure 5.6: Configuration of the network for scenario 2

The results show that there are differences in the solutions depending on the scenario and the supplier. For example in scenario 1 and supplier 1 the location of robots is centralized over a single hospital (H1), and for the rest of scenarios and suppliers the location of robots are decentralized.

Also the deterministic model allows to determine the capacities in units per week for the best configuration (lower cost), for example the capacities for the configuration of scenario 1 and supplier 1 is presented in table 5.5.

Type of robots	Configuration and capacities	
	# of robots	Capacity (units per week)
Preparing unit-doses	5	200000
Storage	3	135000
Preparing prescriptions	3	120000

Table 5.5: Configuration and capacities of robots for sc. 1 and sup. 1

Based on this results, it can be concluded that with 5 robots of preparing unit-doses (cutting robots) each week it's possible to prepare 200000 unit-doses and with 3 robots of storage can be keeped on inventory 135000 unit-doses. Finally, as preparing prescriptions robots are join to the storage robots, the number of this kind of robots is equal to 3 having a capacity to prepare 120000 prescriptions per week.

5.5.3 Stochastic model results

The information of demand of medicines provided by the network of hospitals has been used to generate scenarios over a planning horizon of 7 years which is considered as the time that robots are useful, in this way increments and decrements of the demand in the range -30% + 30% has been considered. The decrements are justified by the tendency of some of the hospitals to specialize in some services, therefore reducing the quantity of patients that can be attended.

As we have used the concept of p robustness, for each scenario of demand, a policy of distribution of prescription and unit doses is obtained, its optimal value is compared with the worst case in order to obtain a common policy feasible over all scenarios (30) which guarantees a p robust value lower than 0.7. The results of the stochastic model are presented in Tables 5.6, 5.7 and 5.8, where economic results are normalized for confidential reasons, for each supplier the same scenarios of overture times were analyzed. Also the distribution network for each scenario are presented in figures 5.7, 5.8 and 5.9.

Supplier 1					
Scenario 1	Objective: 1.00	Unit doses costs: 0.75		Dist. costs: 0.02	Investment: 0.23
	H3	H5	H6		
T1	1	3	1		
T2	1	2	1		
T3	1	2	1		
Scenario 2	Objective: 1.00	Unit doses costs: 0.75		Dist. costs: 0.02	Investment: 0.23
	H1	H3	H5	H6	
T1	1	1	2	1	
T2	1	1	1	1	
T3	1	1	1	1	

Table 5.6: Stochastic model solution location of robots for supplier 1

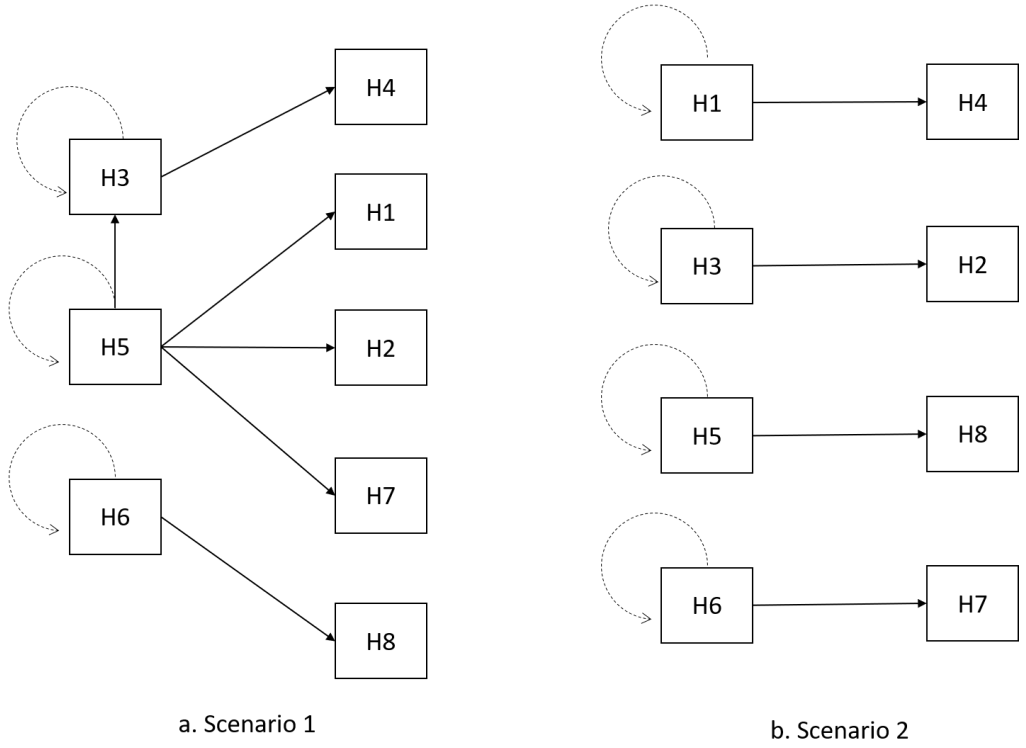

Figure 5.7: Resilient network for supplier 1

Supplier 2					
Scenario 1	Obj.: 1.00	Unit-doses costs: 0.19		Dist.: 0.04	Invest.: 0.77
	H3	H5	H6	H7	
T1	1	4	0	0	
T2	0	0	1	0	
T3	2	8	0	1	
Scenario 2	Obj.: 1.00	Unit-doses costs: 0.2		Dist.: 0.04	Invest.: 0.76
	H2	H3	H5	H6	
T1	0	2	3	0	
T2	0	0	0	0	
T3	1	4	5	1	

Table 5.7: Stochastic model solution location of robots for supplier 2

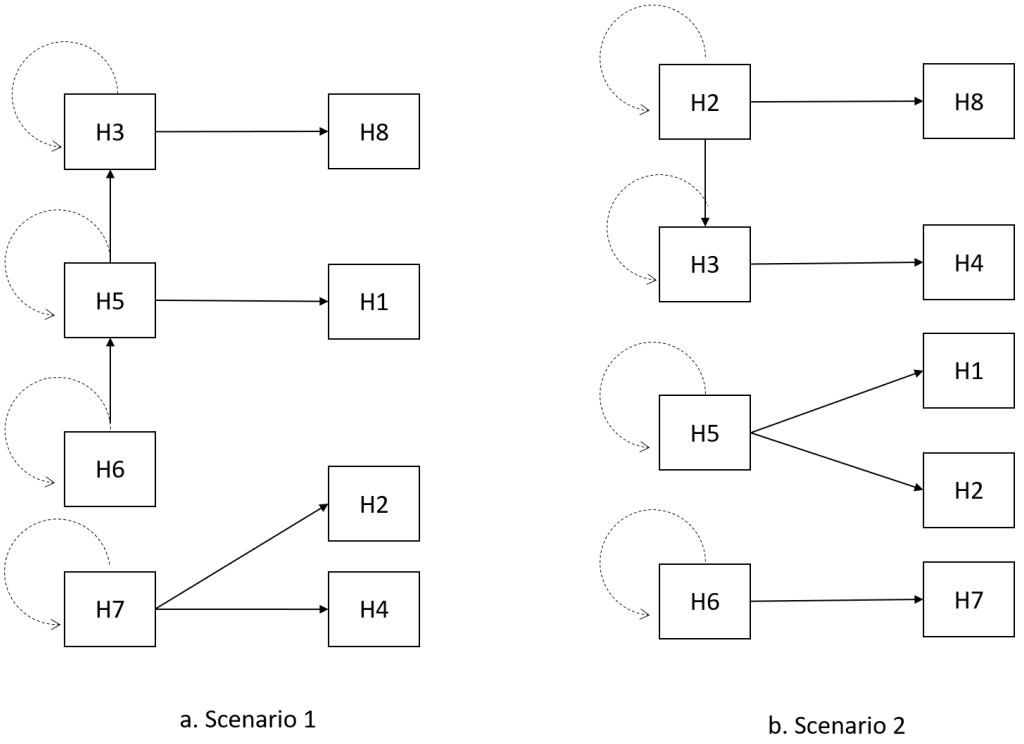

Figure 5.8: Resilient network for supplier 2

Supplier 3					
Scenario 1	Obj.: 150E(-6)	Unit-doses costs: 1		Dist.: 5E(-6)	Invest.: 6.8E-(5)
	H3	H5	H6		
T1	0	5	1		
T2	1	0	1		
T3	0	1	0		
T4	1	0	1		
Scenario 2	Obj.: 1.00	Unit-doses costs: 0.52		Dist.: 0.03	Invest.: 0.45
	H1	H3	H6		
T1	1	1	4		
T2	0	1	0		
T3	1	0	1		
T4	1	1	0		

Table 5.8: Stochastic model solution location of robots for supplier 3

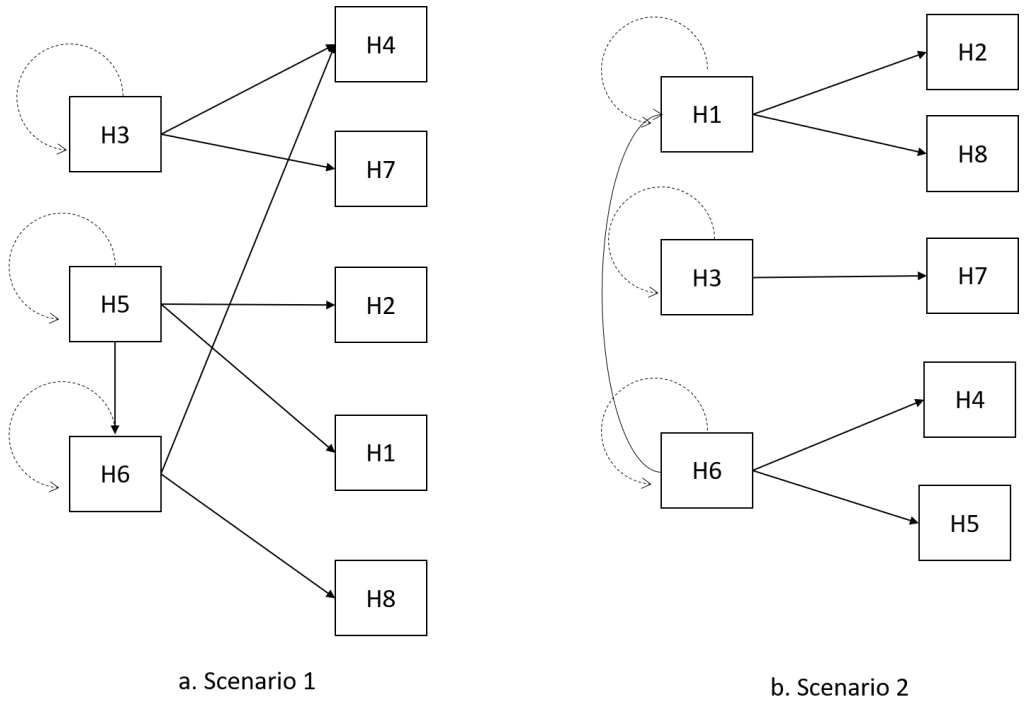

Figure 5.9: Resilient network for supplier 3

It can be observed in table 5.6 that configurations obtained are different between scenarios, due to the use in the second scenario of an extra hospital to locate robots, thus increasing the total costs. In Tables 5.7 and 5.8 results shows that the number of hospitals used are the same but using different locations and configurations.

On the other hand, it can be concluded that for both scenarios at least 3 hospitals are used to locate robots and each hospital where robots are located satisfy its own demand and support other hospitals even if they have robots. Depending of the supplier and the scenario the configuration obtained is different. For supplier 1, in scenario 1, the hospital (H5) is in charge of distributing prescriptions over 4 hospitals and itself, one of these hospitals (H3) has robots. The hospitals H3 and H8 satisfy the demand of hospitals H4 and H8 respectively. For supplier 1 in scenario 2 the network configuration changes, the distribution of unit-doses is one to one, H1, H3, H5 and H6 distributes prescriptions to hospitals H4, H2, H8 and H7 respectively. The results for supplier 2 shows that in scenario 1 hospital H7 distributes to hospitals H2, H4 and itself, hospital H6 only satisfy its own demand and distribute prescriptions to H5 which also distribute prescriptions to hospitals H3 and H1. Finally, H3 satisfy its own requirements and those for hospital H8. For the second scenario, H2 satisfy its own demand and the demand of hospital H8 and support H3 which satisfy the demand of H4, H6 satisfy the demand of H7 and H5 distribute prescriptions to hospitals H1 and H2. Finally for supplier 3, in scenario 1,

each hospital has assigned at least two hospitals, H3 satisfy the demand of hospitals H4 and H7, H5 support H6 and satisfy the demand of H2 and H1 and H6 also satisfy the demand of H4 (as H3 does) and H8. Finally for scenario 2, H1 distribute to hospitals H2 and H8, H3 distribute to H7 and H6 support H1 and distribute to H4 and H5.

By comparing the deterministic and the stochastic results it can be observed the influence of the resilience constraints over the results obtained by the stochastic version. In the stochastic model all the configurations have at least two hospitals that distributes medicines to the rest hospitals of the network. Also, and except for one scenario, the distribution of prescriptions is made by hospitals where also are located robots, therefore the capacities located in some hospitals are enough to satisfy the requirements of other hospitals and to support those where capacities are not enough to distribute over the network. Another difference is that in the deterministic model results, a possible configuration of the network is to locate robots over a hospital which don't distribute prescriptions to other hospitals (see supplier 2 of figure 5.5).

5.6 Conclusions

In this chapter deterministic and stochastic optimization approaches were used to develop a real case application of optimization in the automating process of preparing, storage and dispatching prescriptions and unit-doses in a network of hospitals, where location-allocation of pharmacy robots decisions are evaluated. The concept of p-robustness has been used to model the uncertainty in demand. The concept of multi-source resilience strategy also has been considered in the model to avoid the risk in the distribution of medicines and prescriptions in the healthcare network. A real life instance were solved through several experiments comparing the solutions of the deterministic model with the solutions of the stochastic model.

The deterministic and stochastic models proposed can be implemented to make long term decisions about automatic dispensing medicines systems and distribution of medicines across a hospital network which can have a positive impact on the service offered to patients.

Chapter 6

Prediction of pharmaceutical expenditure in chronic diseases using machine learning models

Contents

In this chapter different models based on machine learning techniques are presented to estimate the pharmaceutical expenditure associated to a chronic disease (diabetes). Different models are used in two different stages. In the first stage five different machine learning models were used: generalized linear model, deep learning, random forest, gradient boosted trees and support vector machines. The machine learning models were combined with additional techniques: (i) feature selection, (ii) boosting and (iii) optimized support vector machine. The second stage consists in the addition of two new variables to the data base: the Charlson index and the number of comorbidities, these variables were calculated based on the condition of each patient of the data base. With this new information the same models used in the first stage are used in the second stage in order to analyze the impact of the comorbidity in the performance of the machine learning models to estimate the pharmaceutical expenditure.

6.1 Introduction

Healthcare is one of the most important issues in the global economies due to the increasing expenditure per capita caused by demographic and epidemiological changes. Healthcare expenditures can be up to 9.95% of the world's total gross domestic product generating huge challenges for public and private health services like the managing of budgets [Carreras 2016].

One of the biggest problems in healthcare is related with the high cost of illnesses that is expected to increase over the pass of the years. Improving the health services to the population can directly become in an economic improvement because it is suitable for workers and inhabitants to be healthy than unhealthy population [Council 2001]. In this way, the health systems become a priority for each country due to its objective of prevention, diagnosis and treatment. Depending on the situation, it could be necessary to estimate the individual cost of treatment or the episode care cost. With this type of information, hospital's managers could be able to improve the planning of resources according the the patientâs needs. Another problem faced by the health systems is the disproportionately expenditures generated by a small portion of the population resulting in a high-cost high-need patients because of its spending concentration. Some of these population can be classified as highly prevalent comorbid chronic condition profile, in this way a correct planning of resources becomes an objective for healthcare managers and organizations [Garfinkel 1988].

Diabetes Melitus is a very common chronic metabolic disease that commonly is presented over people of middle and old age but nowadays incidences are also presented in children [Woldaregay 2019], [Kaur 2019]. This illness is classified as one of the fast growing chronic disease and almost 8.5% of the global population is affected by Diabetes [WHO 2017]. It is defined as the increase of levels of glucose in the blood because of its non outreach to the cells present in the body. Given this, it is also important to emphasize that the amount of monetary resources used to treat patients with diagnoses of Diabetes is very high given the severity, progression and the type of medicines used [Simon 2005]. Diabetes is one of the diseases that produces the most public/private expenditure within system organizations, affects family budgets and is one of the diseases that implies more risk of chronic non transmissive diseases appearing, e g chronic kidney disease and Alzheimerâs disease, and also increases the risk of associated infections It has a strong impact as a high Social Security System cost on the Health System with its growing worldwide trend, especially in developing countries [Https://www.diabetesatlas.org/en/ 2019].

Chronical diseases implies a high pharmaceutical expenditure due to its complexity of treatments and the medicines used. For this reason, the prediction of the pharmaceutical expenditure of these type of illnesses allows a better management of medicines and budgets. Diabetes is one of the diseases that produces the most

public/private expenditure within system organizations, affects family budgets and is one of the diseases that implies more risk of chronic non transmissive diseases appearing, e.g chronic kidney disease and Alzheimer's disease, and also increases the risk of associated infections. It has a strong impact as a high Social Security System cost on the Health System with its growing worldwide trend, especially in developing countries [Federation 2019].

In this context, the pharmaceutical expenditure associated to this type of diseases becomes and important task for managers in hospitals due to its impact in the managing of budgets. For this reason, the main purpose of this chapter is to predict the pharmaceutical expenditure of Diabetes and comorbidities associated by using machine learning models.

6.2 Background

Nowadays, artificial intelligence and specially machine learning models have been used for analysis of high dimensional data becoming a rapidly growing field in the application in different areas. Given that data of population in hospitals and healthcare centers is increasing therefore the knowledge about patients is also higher. In this way the application of machine learning in healthcare is also an emerging area. In this way, in this section are presented methods developed in the literature for predicting pharmaceutical expenditure and methods for modeling and predicting diabetes.

[Caballer-Tarazona 2019] developed a cross-sectional study for predicting healthcare expenditure in a district of Spain based on multimorbility group. Using public databases, authors obtain information related to: sex, costs of hospitalization, surgery, outpatient consultations, laboratory, oncology care, and other types of services managed by the hospitals. With this information authors proposed the use of logistic regression with two phases that corresponds to two interrelated models. The first model is modeled using a logit model for determining the probability of a greater than 0 and the second model obtains the estimation of the costs throw the use of the Manning and Mullahy algorithm. Using a statistical test the explanatory variables are evaluated and some statistics are used to evaluate the performance of the results (Root Mean Squared Error, Mean Absolute Percentage Error, Medium Absolute Percentage Error and coefficient of determination). Results of the proposed models shows that on average can be obtained coefficients of determination between 33% and 48%.

A similar study was developed by [Mujasi 2015]. The aim of this study is to analyze and identify the main predictors for pharmaceutical expenditure in different districts with the objective of determining the appropriate budget for each zone. The variables used for creating the model were related with population characteristics, health system characteristics and health behavior. The authors perform an

uni-variant descriptive analysis and a bi-variant descriptive and inferential analysis too for measuring the correlation between variables. With these analyses, they perform an econometric analysis for testing regression models obtaining different values that can help to decision makers to understand the behavior of the pharmaceutical expenditures.

In the same idea of expenditure prediction and control, [Quercioli 2018] developed a cross-sectional study in three phases: collection of health status information in a province of Siena, collection of health expenditure and statistical analysis of these information. To develop the statistical analysis, authors perform a square root transformation of the total health expenditure and a z-standardization of the continuous variables for proposing a new index of pharmaceutical expenditure. The findings shows that disease severity is a better predictor than the risk of death measure and the health expenditure is influenced by physical areas of perceived health. In a similar way [Lauridsen 2010] perform a regression model for public pharmaceutical expenditure for 50 provinces in Spain. They analyze the effects of spatial association using a non parametric filtering approach that helps to identify the main variables that affect the pharmaceutical expenditure. With this type analysis and identification of main variables, [Mujasi 2015] also developed a cross sectional study for allocating primary healthcare pharmaceutical budgets to districts.

There are works related with the identification of factors that affects the pharmaceutical expenditure. [Mousnad 2014] developed a systematic review that allow readers to identify different methodologies to determine the factors that increase the pharmaceutical expenditure. In conclusion most of the articles uses statistical methods to identify the main factors. Some of the factors that contribute to increase the pharmaceutical expenditure are: drug exposure, price of medicines, average growth rate of population, socio-economic status, age, sex, among others. As conclusion of this review, authors affirm that the major cost drivers are changes in medicine quantities, therapies and new medicines.

On the other side, there are works related with the use of machine learning or statistical models for Diabetes rate prediction. For example, [Pollmanns 2019] used an ecological analysis using data from Germany identifying the diabetes hospitalization rates. Authors developed a linear regression and logistic regression analysis for identifying the variables that could help to determine the diabetes rates of hospitalization and for identifying the impact of predictors on the probability for a country to show a rate out of limits of control. The coefficient of determination obtained was 0.568.

Different Machine Learning models for predicting diabetes were tested by [Kaur 2019]. By using a data set of female patients with a minimum age of 21 years old in India. The main idea of the research was to identify an early diagnosis of diabetes based on 9 different types of variables using 6 type of machine learning models. Different evaluation parameters were obtained such as accuracy, recall,

precision, F1 score and Area Under the ROC Curve (AUC) finding that the best accuracy was obtained by the support vector machine model. A similar study was developed by [Birjais 2019] but using three different techniques, gradient boosting, logistic regression and Naive Bayes with the main idea of improve the diagnosis of diabetes disease. Authors used 8 different types of attributes obtained by an Indian data-base. Authors use the percentage of sensitivity and specificity and the testing accuracy to evaluate the performance of the models finding that the gradient boosting has a higher level of accuracy over the other two models.

6.3 Methods

The general methodology used is this study is described in Figure 6.1

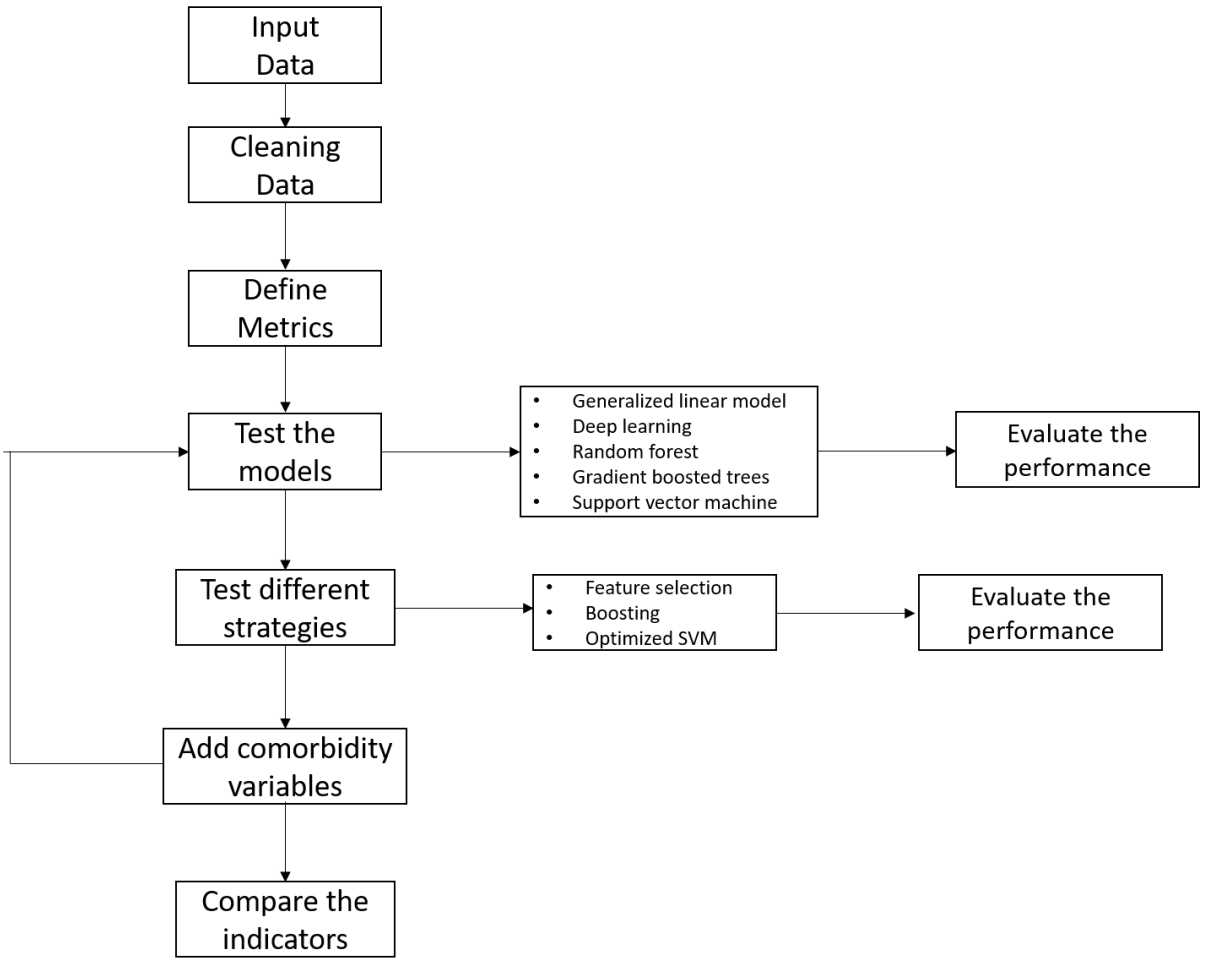

Figure 6.1: Methodology

After the analysis of the anonymized data and the cleaning and missing data imputation (see subsection 6.3.1), the main idea of the methodology in this work is to use machine learning models (generalized linear model, deep learning, random forest, gradient boosted trees and support vector machines) in two different stages. In the first stage the basic models are analyzed with different performance indicators, after that, three different techniques are used for analyzing improvements of the first results (feature selection, boosting and optimized support vector machines). In the second stage new variables related with comorbidity were calculated based on the data collected and added to the database, with these new variables and these new data, experiments are repeated and the performance indicators are evaluated.

6.3.1 Data description

The data used for the present study has been collected by a Colombian Hospital recording patients who have previously been prescribed as patients with diabetes and have arrived at the hospital suffering a comorbidity. The data source used has records for two different years (2017-2018) containing information related with sex, age, date where patient assist to the hospital, medical diagnostic(s), type of affiliation to the Colombian health system (subsidized or contributory given by the Colombian law 1751/2015) and the pharmaceutical expenditure. The pharmaceutical expenditure represent different types of medicines administrated to patients and their costs. In some cases these costs are not homogeneous, it can exist different values for the same patient and the same diagnostic. The data base contains 193.955 records, nevertheless, as one patient can have more than one diagnostic the number of different patients registered decreases to 36392 records. The population is divided into 45% males and 55% females. Respecting to the type of System, 70% of the patients belongs to contributory system (see figure 1.1) while 30% to the subsidized system.

There are 214 different types of illnesses associated to diabetes, on average each patient arrives into the hospital with 1.78 illnesses with a minimum value of 1 and a maximum value of 21. Additionally to this data two new variables based on the information available have been calculated and included in order to improve the forecasting: (i) frequency of medicine consumptions which indicates the number of consumption of medicines of each patient when a treatment is demanded to the hospital and (ii) the number of visits (different dates) a patient requires a service at the hospital.

The data base was cleaned up filling some missing values associated with the type of system of the patient. This situation occurs when a patient has multiple lines (multiple consumption of medicines) but the registration of the type of health system status is only available for the first line, therefore a program has been used to fill this information because a patient has only one type of system.

Variables

Table 6.1 present the description of the variables used is this study.

Variable	Description	Type
Sex	Sex of the patient	M/F (binary)
Age	Age of patients	Integer (years)
Type of affiliation	Type of system to the health system	subsidized/contributory (binary)
Frequency of visits	Number of visits to the hospital	Integer (years)
Frequency of consumption of medicines	Number of different consumptions of medicines	Integer (years)
Type of illness(es) (214)	Type of comorbidity(ies) reported for each patient	Binary (presence or absence)
Pharmaceutical expenditure	Pharmaceutical expenditure for each patient	Real ($)

Table 6.1: Description of variables

6.3.2 Data analysis

Figure 6.2 presents the range of the values of the pharmaceutical expenditure for each patient over two years. These values varies between $262 and $2.217.366.074 Colombian pesos for one patient with an average of $18.657.672.

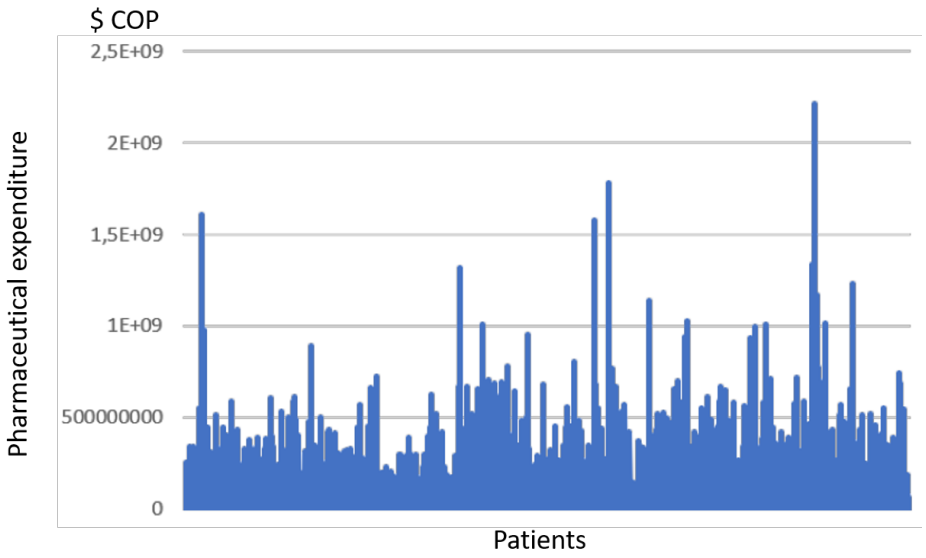

Figure 6.2: Pharmaceutical expenditure of diabetes' patients 2017-2018

Also, for one patient per illness associated with diabetes per visit to the hospital the pharmaceutical expenditure varies between $261 and $206.094.271 Colombian pesos with an average of $2.500.227.

Figure 6.3 presents the boxplot of the pharmaceutical expenditure (in $COP) for each patient over two years. Although the values are concentrated in a region with costs lower than $ 50.000.000 (skewed left), the range is wide, it exists for example an important number of values concentrated around high costs, than can be up to $ 2.000.000.000. This implies that the pharmaceutical expenditure presents a high level of variability.

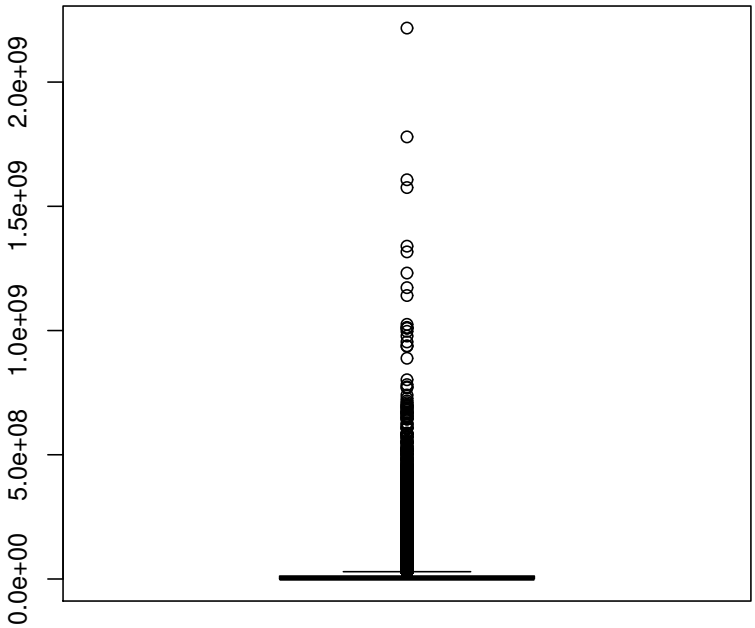

Figure 6.3: Boxplot of pharmaceutical expenditure

Figure 6.4 presents the histogram of the pharmaceutical expenditure distribution for each patient(in $COP) over two years. Most of the data are in the first range of the histogram, nevertheless the range of the data is large which support the conclusion derived by the boxplot presented in figure 6.3.

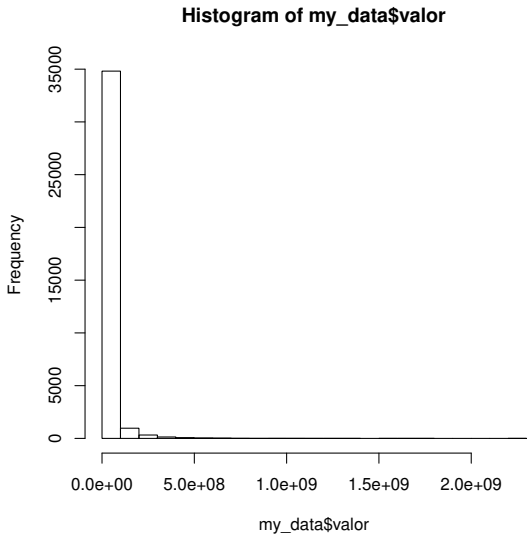

Figure 6.4: Histogram of pharmaceutical expenditure

Figure 6.5 presents the distribution of pharmaceutical expenditure (in $COP) versus age (in years) of each patient over the two years. It can be concluded that the values of pharmaceutical expenditure are mostly concentrated in older patients, this is also supported by the fact that Diabetes is a common disease for older people.

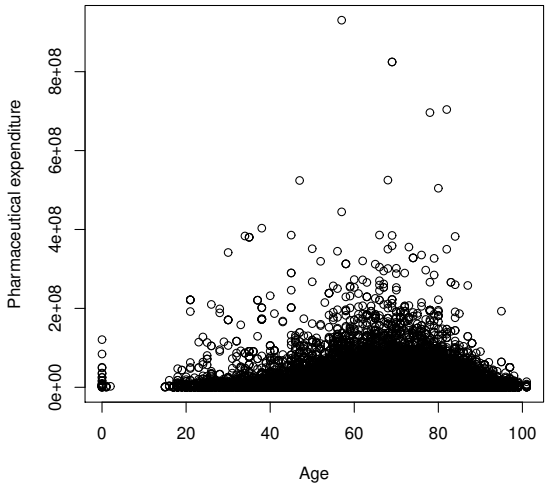

Figure 6.5: Pharmaceutical expenditure versus age

6.3.3 Performance measures

In order to analyze the performance of the models the following metrics are used:

- Root Mean Squared Error: It is a measure of the differences between values (sample or population values) predicted by a model or an estimator and the values observed. This measure is calculated as:

$$\frac{1}{n}\Sigma_{i=1}^{n}(y_i - f_i)^2$$

- Mean Absolute Error: is the amount of error in the measurements. It is the difference between the measured value and true value. This measure is calculated as:

$$\frac{1}{n}\Sigma_{i=1}^{n}|y_i - f_i|$$

.

- Relative Error Lenient: is the ratio of the absolute error of a measurement to the measurement being taken. This measure is calculated as follows:

$$\frac{1}{n}\Sigma_{i=1}^{n}\frac{|y_i - f_i|}{max(|y_i|, |f_i|)}$$

.

- Squared Error: it is a measure that shows how close is the prediction against the real values. This measure is calculated as:

$$\Sigma_{i=1}^{n}(y_i - f_i)^2$$

- Correlation: It is the degree in which the prediction and the real values are related.

Where n is the number of observations, y_i the observed value and f_i the predicted value.

6.3.4 Machine learning models

As the main purpose of this chapter is to build a model for predicting the pharmaceutical expenditure, different machine learning models have been used to have a preliminary prediction. In this way, the following models have been used:

- Generalized Linear Model [Hastie 1990]: correspond to a generalization of the linear regression but it allows that the response variables errors can have distributions different to the normal distribution. This model uses the following equation:

$$n_i = B_0 + B_1 * x_{1i} + ... + B_n * x_{ni}$$

Where n_i corresponds to the response value, in this case the pharmaceutical expenditure and B_i the coefficients obtained by the regression model when using the x_{ni} input variables represented in this case by the variables described in table 6.1.

- Deep Learning [Schmidhuber 2015]: is a method based on artificial neural networks that use multiple layers for extracting features from the inputs in this case the variables described in table 6.1, the idea is to have a high number of hidden layers that enables to predict accurate values of the response variables in this case the pharmaceutical expenditure, the following figure represents a model of deep learning:

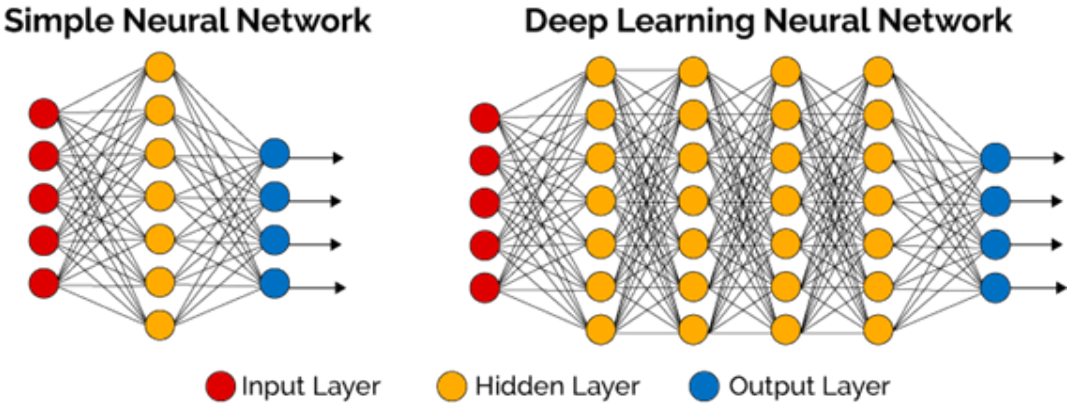

Figure 6.6: Example of deep learning [Rosebrock]

- Random Forest [Breiman 2001]: is composed by multiple tree predictors in which the main idea is to learn very highly irregular patterns and build the classification or prediction by obtaining the average of the multiple deep decision tress. The main procedure is to generate tree models where variables are selected in this case the variables described in table 6.1, and for each kth tree a random vector Θ_k is generated, then the random forest is a collection of of tree models $h(x, \Theta_k)$ where each tree has a weighted value.

- Gradient Boosted Trees [Mason 1999]: this technique produces a prediction model in the form of an ensemble of weak prediction models, in which each new tree is a fit on a modified version of the original data set, the Gradient Boosted Trees use the following equations:

$$y_i^t = \sum_{k=1}^{t} f_k(x_i) = y_i^{t-1} + f_t(x_i)$$

Where y_i^t is the model trained in round t that represents the prediction of the pharmaceutical expenditure, y_i^{t-1} the functions added in the previous rounds

and $f_t(x_i)$ the new function added that considers in this case the variables described in table 6.1.

- Support Vector Machine [Vapnik 2000]: is a supervised learning method that use a function of classification for partitioning the data into categories. The Support Vector Machine uses the following function:

$$W = C * \sum_{i=1}^{N} L(y_i, F(x_i)) + \sum_{j=1}^{P} B_j^2$$

Where x_i corresponds to the inputs in this case the variables explained table 6.1, $L(.)$ is the loss function, B are the coefficients of the regularization term when considering P predictors (the predictors are associated with variables of sex, age, type of system,...) and the constant C is the error penalty of the model. Also, the function $F(.)$ is a prediction equation for the pharmaceutical expenditure that can be defined as follows:

$$F(x) = \sum_{i=1}^{N} \alpha_i * \varphi(x) + B_0$$

Where α_i is the linear kernel function used to transform the input data to the required forms of relationships and B_0 a constant.

Results

Tables 6.2, 6.3, 6.4, 6.5, and 6.6 present the results of the different machine learning models for each performance measure and its standard deviation.

Model	**Root Mean Squared Error**	**Standard Deviation**
Generalized Linear Model	47735428.028	+/- 7435069.005
Deep Learning	47165735.786	+/- 4860949.285
Random Forest	54994912.257	+/- 7728244.132
Gradient Boosted Trees	45401130.757	+/- 8336406.965
Support Vector Machine	55412684.408	+/- 7282307.490

Table 6.2: Root Mean Squared Error

Model	Mean Absolute Error	Standard Deviation
Generalized Linear Model	17339900.689	+/- 623678.019
Deep Learning	16909068.925	+/- 533221.932
Random Forest	23341173.787	+/- 780766.312
Gradient Boosted Trees	15544911.101	+/- 793509.151
Support Vector Machine	24163221.134	+/- 1213923.578

Table 6.3: Mean Absolute Error

Model	Relative Error Lenient	Standard Deviation
Generalized Linear Model	0.8132	+/- 0.68%
Deep Learning	0.6998	+/- 0.54%
Random Forest	0.7576	+/- 0.21%
Gradient Boosted Trees	0.6557	+/- 0.64%
Support Vector Machine	0.7623	+/- 0.46%

Table 6.4: Relative Error Lenient

Model	Squared Error	Standard Deviation
Generalized Linear Model	2322895289882560	+/- 688778331766103.400
Deep Learning	2243509694607950	+/- 461921813118369.440
Random Forest	3072220980059220	+/- 842448833613135.900
Gradient Boosted Trees	2116859218857420	+/- 769622667971187.400
Support Vector Machine	3112991195237140	+/- 807425914950682.600

Table 6.5: Squared Error

Model	Correlation	Standard Deviation
Generalized Linear Model	0.568	+/- 0.071
Deep Learning	0.582	+/- 0.026
Random Forest	0.549	+/- 0.035
Gradient Boosted Trees	0.589	+/- 0.072
Support Vector Machine	0.338	+/- 0.043

Table 6.6: Correlation

Based on these results it can be concluded that the model with the best performance over the five key performance indicators (Root Mean Squared Error, Mean Absolute Error, Relative Error Lenient, Squared Error and Correlation) corresponds to the Gradient Boosted Trees model. For a better understanding of the performance of the models, in Figures 6.7, 6.8, 6.9, 6.10 and 6.11 are presented the charts of the contrast between the predicted pharmaceutical expenditure (PE) in $ COP generated by each model and the real values.

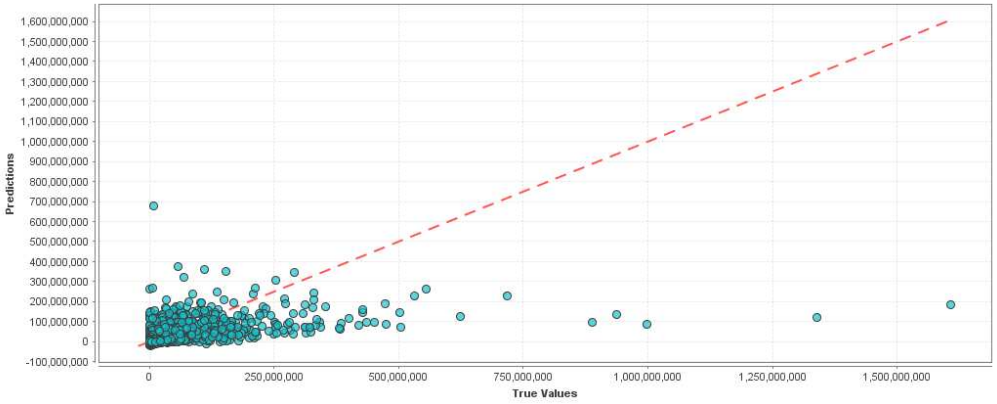

Figure 6.7: Chart of the predicted PE Generalized Linear Model versus real data

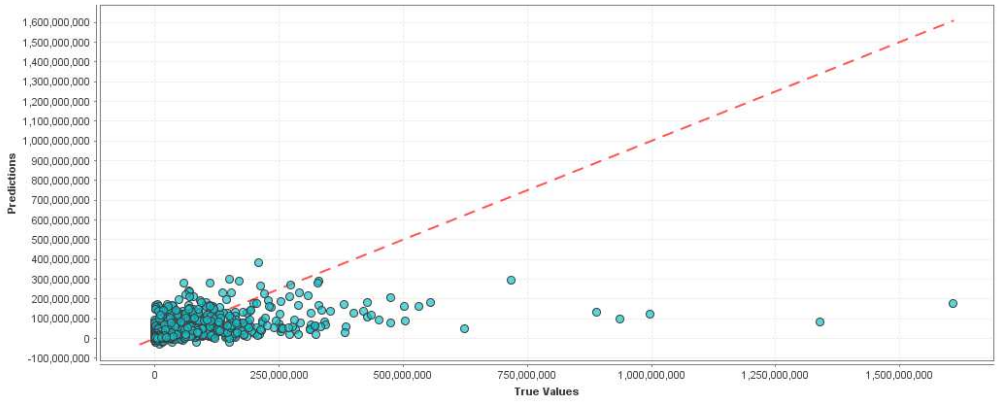

Figure 6.8: Chart of predicted PE Deep Learning versus real data

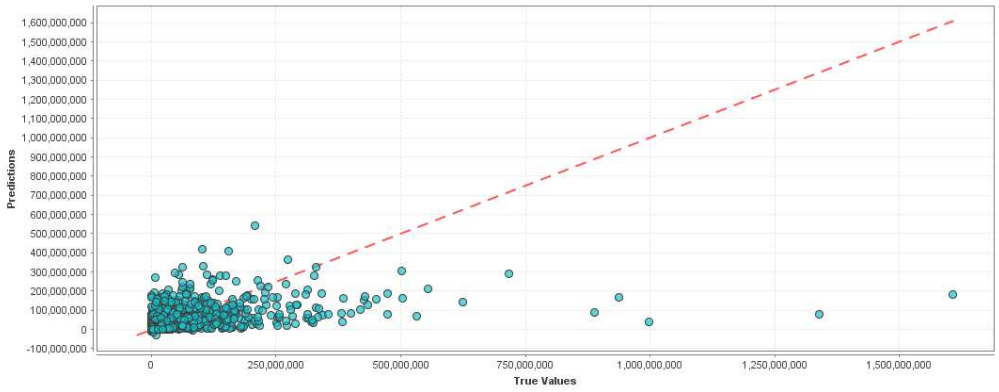

Figure 6.9: Chart of predicted PE Random Forest versus real data

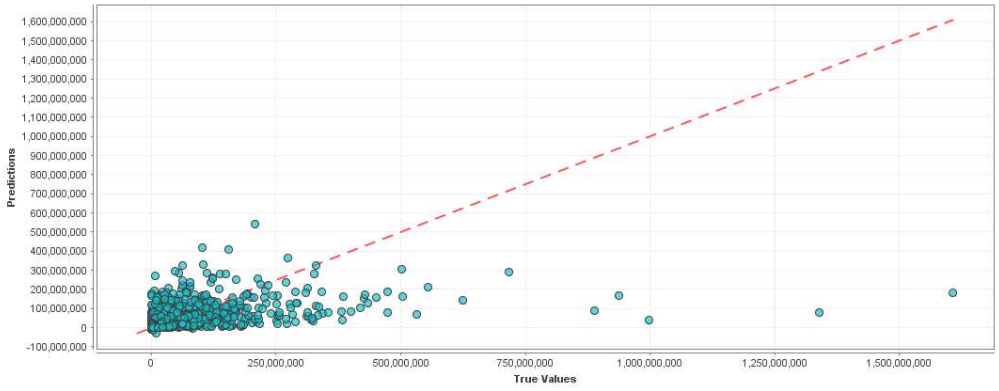

Figure 6.10: Chart of predicted PE Gradient Boosted Trees versus real data

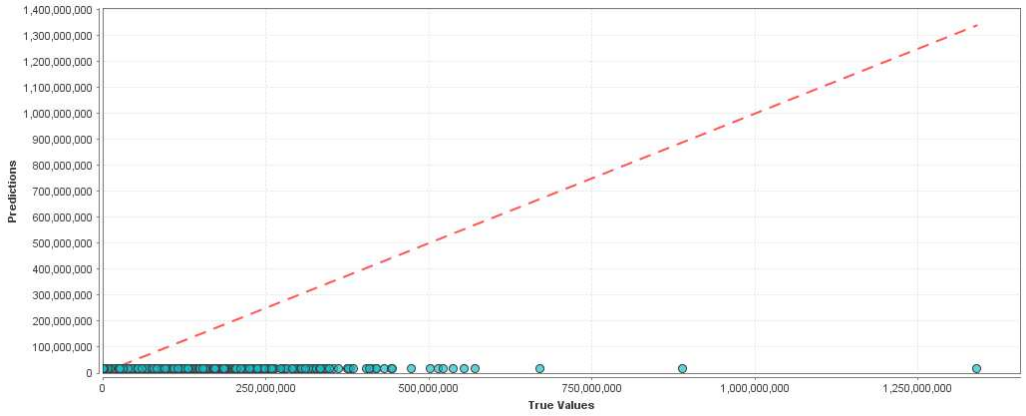

Figure 6.11: Chart of predicted PE Support Vector Machine versus real data

From the previous figures, it can be concluded that with exception of the support vector machine model, the performance of the different models are at least graphically similar because these models can predict the same area of prediction values, nevertheless the support vector machine model only can predict values with low pharmaceutical expenditure. Given these results it can be concluded that over the performance indicators the Gradient Boosted Trees model presents the best results.

6.3.5 Machine learning models with feature selection

In order to improve the performance of the machine learning models obtained in the previous section, a feature selection technique was used. The feature selection technique helps to determine the most relevant features in a regression or classification problem [Khaire 2019]. The main idea of feature selection is to identify features which are not providing useful information and those which are not providing more information that the current ones (denominated as irrelevant and redundant respectively). In this case each feature corresponds to the variables described in table 6.1. In this way, a combined forward selection technique was used. The feature selection algorithm is as follows:

Algorithm 1 Feature selection algorithm [Khaire 2019]

procedure FEATURE SELECTION
$FS^{(0)} = 0; F^{(0)} = \{f_1, f_2, ..., f_n\}; i = 0; opt = 0; iter = 0;$
while $i < n$
    k=size($F^{(i)}$;
    max=0;
    feature=0;
    for j=1 to k
    score=eval($F_j^{(i)}$);
    if $score > max$;
    max=score; feature=$F_j^{(i)}$;
    end-if
    end-for
    if $max > opt$
    opt=max; iter=i;
    end-if
    $FS^{(i+1)}$ ←FS$^{(i)}$ + feature
    $F^{(i+1)}$ ←F$^{(i)}$ - feature
end-while
=0

Results

The models were tested again including the feature selection, the results for each performance measure are presented in Tables 6.7, 6.8, 6.9, 6.10, and 6.11.

Model	Root Mean Squared Error	Standard Deviation
Generalized Linear Model	46155352.794	+/- 6655501.025
Deep Learning	40876976.359	+/- 4159846.285
Random Forest	53487021.168	+/-75007659.132
Gradient Boosted Trees	52464941.089	+/- 8416370.126
Support Vector Machine	55358623.748	+/- 7287405.821

Table 6.7: Root Mean Squared Error

Model	Mean Absolute Error	Standard Deviation
Generalized Linear Model	17622331.037	+/- 787578.407
Deep Learning	12227186.157	+/-468258.531
Random Forest	18451267.509	+/-431398.984
Gradient Boosted Trees	17853497.598	+/- 7449112.148
Support Vector Machine	23925826.134	+/- 1213923.578

Table 6.8: Mean Absolute Error

Model	Relative Error Lenient	Standard Deviation
Generalized Linear Model	0.6902	+/- 0.48%
Deep Learning	0.6525	+/- 0.51%
Random Forest	0.6738	+/- 0.58%
Gradient Boosted Trees	0.6733	+/- 0,61%
Support Vector Machine	0.7623	+/- 0.46%

Table 6.9: Relative Error Lenient

Model	Squared Error	Standard Deviation
Generalized Linear Model	2165753146610370	+/- 631870990446783.600
Deep Learning	1983980493135700	+/- 414567421456785.465
Random Forest	2880922753326300	+/- 527905321103420
Gradient Boosted Trees	2809238272371500	+/- 837882795474225.600
Support Vector Machine	3107062250100940	+/- 807185229098870.100

Table 6.10: Squared Error

Model	Correlation	Standard Deviation
Generalized Linear Model	0.599	+/- 0.040
Deep Learning	0.590	+/-0.021
Random Forest	0.641	+- 0,070
Gradient Boosted Trees	0.645	+/- 0.061
Support Vector Machine	0.372	+/- 0.035

Table 6.11: Correlation

Based on these results it can be concluded that the performance is improved in most of the models for most of the performance indicators. Gradient Boosted Trees is the only model that can not reach an improvement by including the feature selection (reaching an improvement only in the correlation indicator). The mean absolute error measure of the generalized linear model and the relative error lenient measure of the support vector machine model were not reduced.

In general, the best improvement obtained is for the Deep Learning model: the Root Mean Squared Error was reduced by 13.33%, the Mean Absolute Error was reduced by 21.34% the Relative Error Lenient was reduced by 6.76%, the squared error was reduced by 6.28% and the correlation was increased by 0.17%. The comparison between the performance indicators obtained for the deep learning model without feature selection and those obtained by the deep learning model with feature selection are presented in table 6.12.

Performance measure	D.L without feature selection	D.L with feature selection	% of improvement
Root mean squared error	47165735.79	40876976.36	13.33%
Mean absolute error	15544911.1	12227186.16	21.34%
Relative error lenient	0.6998	0.6525	6.76%
Squared error	2.11686E+15	1.98398E+15	6.28%
Correlation	0.589	0.590	0.17%

Table 6.12: Comparison of deep learning performances without and with feature selection

6.3.6 Machine learning models with boosting strategy

In order to improve the results obtained by the previous methods another strategy named Boosting was used to reduce the variability of results. The strategy of Boosting consists in combining different methods in the training phase to improve the performance of prediction and reduce the variability, this method divide the training set into subsets in which a learning algorithm is used and when a new in-

stance is added, the number of classifiers is counted for adding this new instance into those with highest values, in this way boosting method learns slowly an in each iteration, a model is fitted with respect to the residuals of the model and with this new information is added to the fitted function, after all the process for each model a weight is generated and used for improving the regression or classification [Moral-García 2020], [Breiman 1996]. The graphical description of boosting method is presented in Figure 6.12.

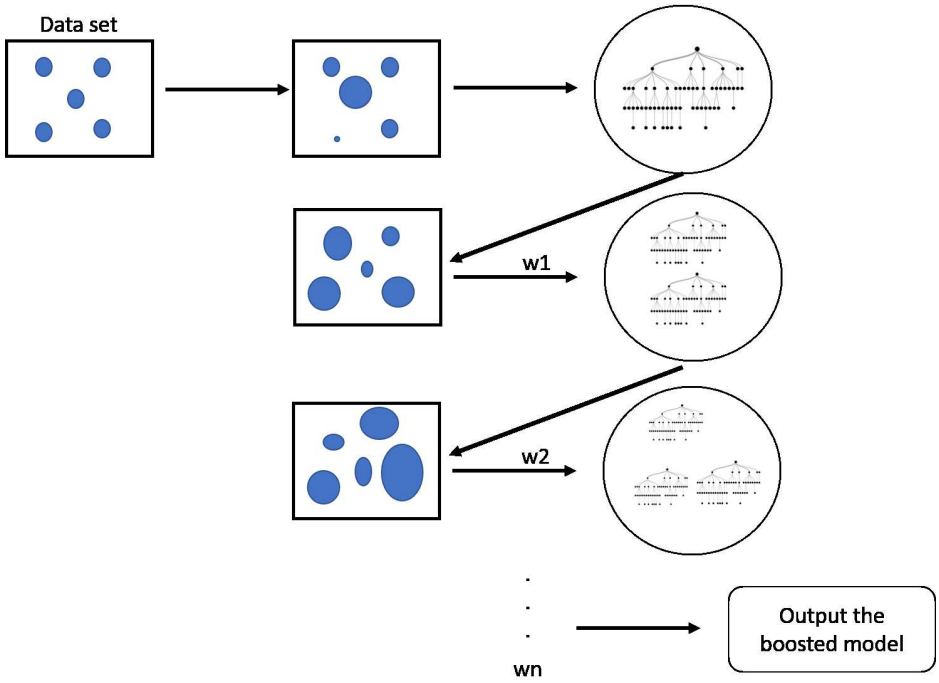

Figure 6.12: Boosting method description

The pseudo-code of the boosting strategy is as follows:

Algorithm 2 Boosting algorithm [Mason 1999]

0: **procedure** BOOSTING
x_i are the variables and ;y the response variable (pharmaceutical expenditure);
$w_i = \frac{1}{n}$ for all the training points
0: **for** i=1 to M
0: fit a regression tree according to w_i
0: compute the residuals r_{im}=(observed-predicted)
0: predict the residuals r_t
0: update the prediction with the selected algorithm
=0

Results

In this way, the machine learning models were combined with Decision Trees to improve their performance indicators. Tables 6.13, 6.14, 6.15, 6.16, and 6.17 present the results of the performance indicators for all models.

Model	Root Mean Squared Error	Standard Deviation
Deep Learning	40716937.178	+/- 0.000
Random Forest	49034857.658	+/- 0.000
Gradient Boosted Trees	48716937.178	+/- 0.000
Support Vector Machine	48681406.049	+/- 0.000

Table 6.13: Root Mean Squared Error

Model	Mean Absolute Error	Standard Deviation
Deep Learning	11527546.613	+/- 45827722.734
Random Forest	17215126.430	+/- 45113148.657
Gradient Boosted Trees	16527546.613	+/- 45827722.734
Support Vector Machine	16521909.181	+/- 45791984.144

Table 6.14: Mean Absolute Error

Model	Relative Error Lenient	Standard Deviation
Deep Learning	0.6636	+/- 0.29%
Random Forest	0.6263	+/- 0.28%
Gradient Boosted Trees	0.6636	+/- 0.29%
Support Vector Machine	0.6633	+/- 0.29%

Table 6.15: Relative Error Lenient

Model	Squared Error	Standard Deviation
Deep Learning	2373339968028839.500	+/- 32831406617709624
Random Forest	2404417265497991.500	+/- 34181195922015544
Gradient Boosted Trees	2373339968028839.500	+/- 32831406617709624.000
Support Vector Machine	2369879294869495.500	+/- 32807598646025208.000

Table 6.16: Squared Error

Model	Correlation	Standard Deviation
Deep Learning	0.610	+/-0.010
Random Forest	0.672	+- 0,001
Gradient Boosted Trees	0.520	+/- 0.000
Support Vector Machine	0.510	+/- 0.000

Table 6.17: Correlation

Based on these results it can be concluded that the boosting method decrease the variability associated with the root mean squared error for all models. Also, the results show that the boosting strategy reduce the root mean squared errors for all models. For the root mean squared error the best improvement is reached for the support vector machine with a reduction of 13.72%. On the other hand the results of the variability of the mean absolute errors are not improved but their performance are improved for all models. The best improvement for mean absolute error is reached for the support vector machine model with a reduction of 30.95%. All models improve the performance and the variance of the error lenient. For the squared error measure, the results show that the variance can't be improved for any model. Finally, the standard deviation of the correlation is reduced for all models and the performance of this measure is improved for all models except for the gradient boosted trees.

The best results in this phase are obtained again by the deep learning model: the Root Mean Squared Error was reduced by 0.39%, the Mean Absolute Error was reduced by 5.32% the Relative Error Lenient was increased by 1.70%, the Squared Error was increased by 19.63% and the Correlation was increased by 3.39%. Table 6.18 presents the comparison of the performance measures between deep learning with feature selection and deep learning with boosting strategy.

Performance measure	D.L with feature selection	D.L with boosting	% of improvement
Root mean squared error	40876976.36	40716937.18	0.39%
Mean absolute error	12227186.16	11527546.61	5.72%
Relative error lenient	0.6525	0.6636	-1.70%
Squared error	1.98398E+15	2.37334E+15	-19.63%
Correlation	0.590	0.610	3.39%

Table 6.18: Comparison of deep learning with feature selection and deep learning with boosting

6.3.7 Optimized machine learning model

In order to speed up the process of convergence of machine learning models and to improve their performance measures, a combination of optimization with machine learning models has been developed. Some search methods for the support vector machine model are based in optimization techniques such as quadratic programing or gradient descent, the exploration of evolutionary algorithms to optimize the parameters of the machine learning model in the training phase. Based on this, the optimization problem is [Mierswa 2006]:

$$minimize = \frac{1}{2}||w||^2 + C * \sum_{i=1}^{n} \xi_i \tag{6.1}$$

Subject to:

$$y_i(\langle w, x_i \rangle + b) \geq 1 - \xi_i \qquad \forall i \tag{6.2}$$

In this way, the optimized machine learning strategy used in this work is as follows:

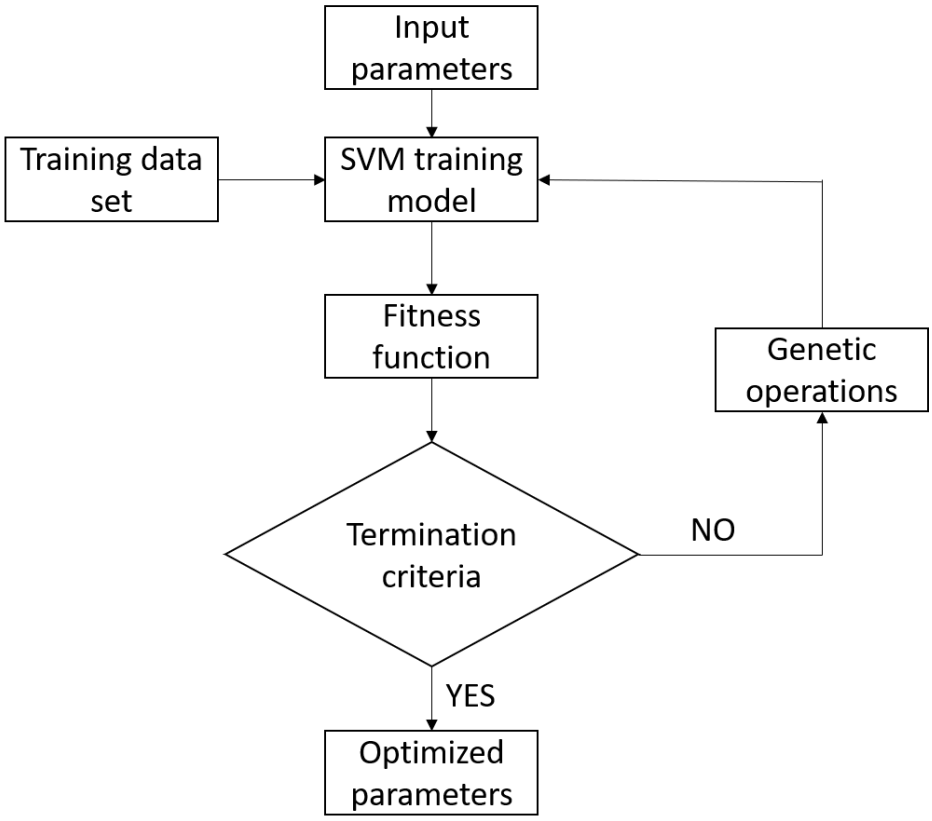

Figure 6.13: Optimized machine learning strategy [Dantas Dias 2016]

The strategy used consists in iteratively improves the parameters of the support vector machine model by evaluating the fitness functions that corresponds to the prediction of the pharmaceutical expenditure, this fitness function is embedded in an evolutionary algorithm over the set of data until no more improvements can be reached.

The use of the support vector machines implies the use of a Kernel function. The idea of the Kernel function is to transform data into the adequate form for processing in the training phase, therefore this function is applied over each data instance to transform the data into a high dimensional-space which could lead to separate the data. The Kernel function is defined mathematically as $Kx, y = \langle f(x), f(y) \rangle$ where x and y are the inputs. Different Kernel functions to analyze the performance have been used:

- Radial
$$K(x_i, x_j) = exp(-\frac{||x_i - x_j||^2}{2\sigma^2})$$
where x_i, x_j are the inputs, in this case the variables described in table 6.1.

- Polynomial
$$K(x_i, x_j) = (x_i.x_j + 1)^d$$
where d is the degree of the polynomial and x_i, x_j are the inputs, in this case the variables described in table 6.1.

- Anova
$$K(x, y) = \Sigma_{i=1}^{n} exp(-\sigma(x^k - y^k)^2)^d$$
where d is the degree of the polynomial and x_i, x_j are the inputs, in this case the variables described in table 6.1.

- Epanechnikov
$$K(u) = \frac{3}{4}(1 - u^2) and |u| \leq 1$$
where u is the mean of the data normalized.

- Multiquadratic
$$K(x_i, x_j) = \sqrt{||x - y||^2 + c^2}$$
where c is the intercept constant and x_i, x_j are the inputs, in this case the variables described in table 6.1.

Results

Figures 6.14, 6.15, 6.16, 6.17 present the results for the different Kernel functions used.

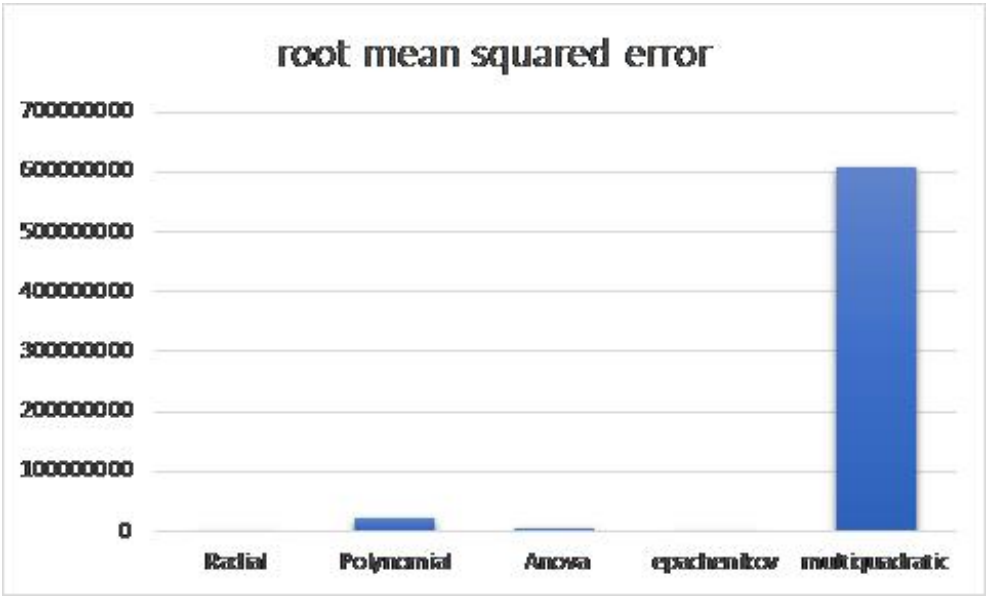

Figure 6.14: Results optimized root mean squared error

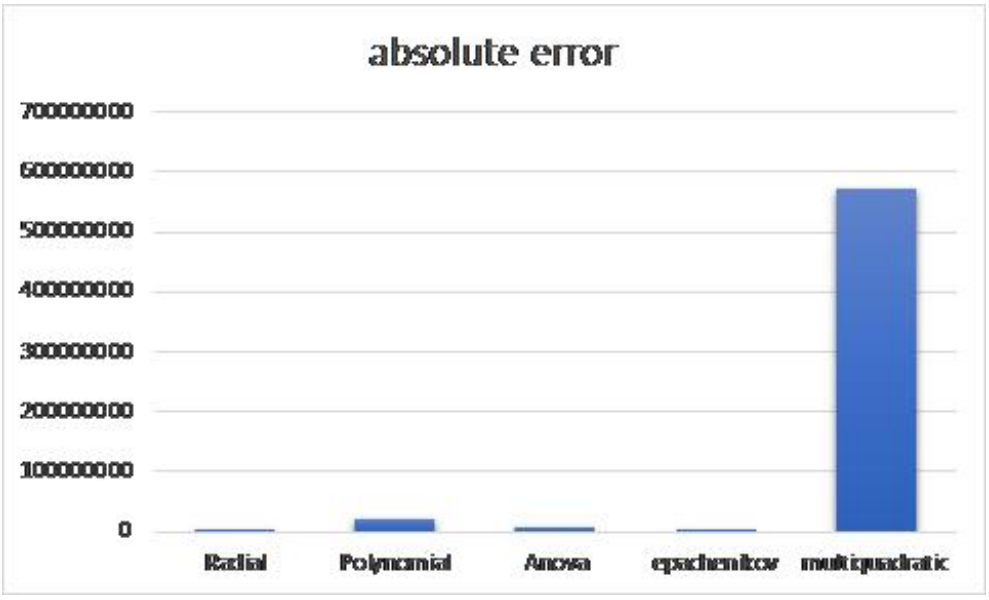

Figure 6.15: Results optimized mean absolute error

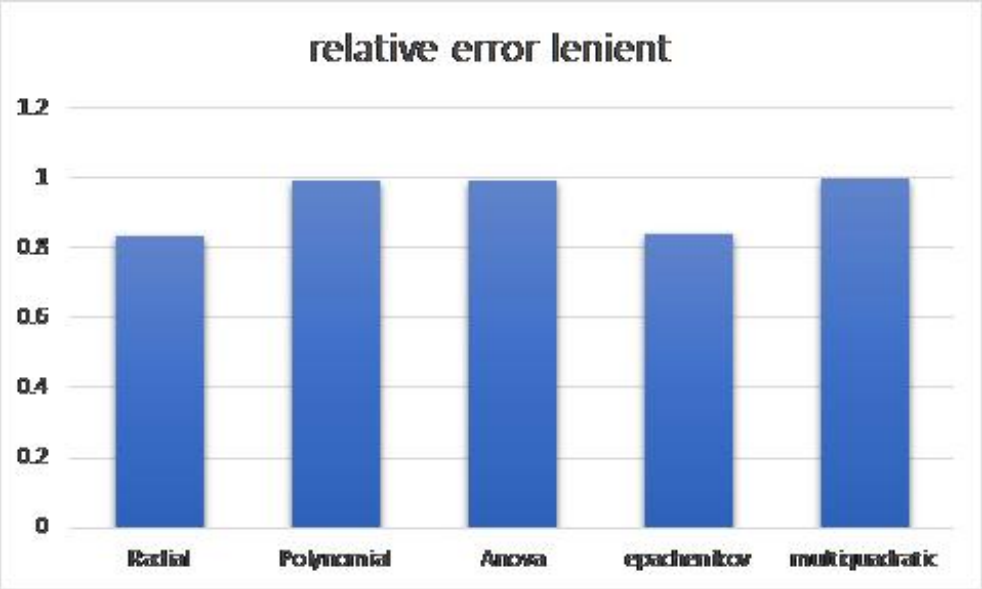

Figure 6.16: Results optimized relative error lenient

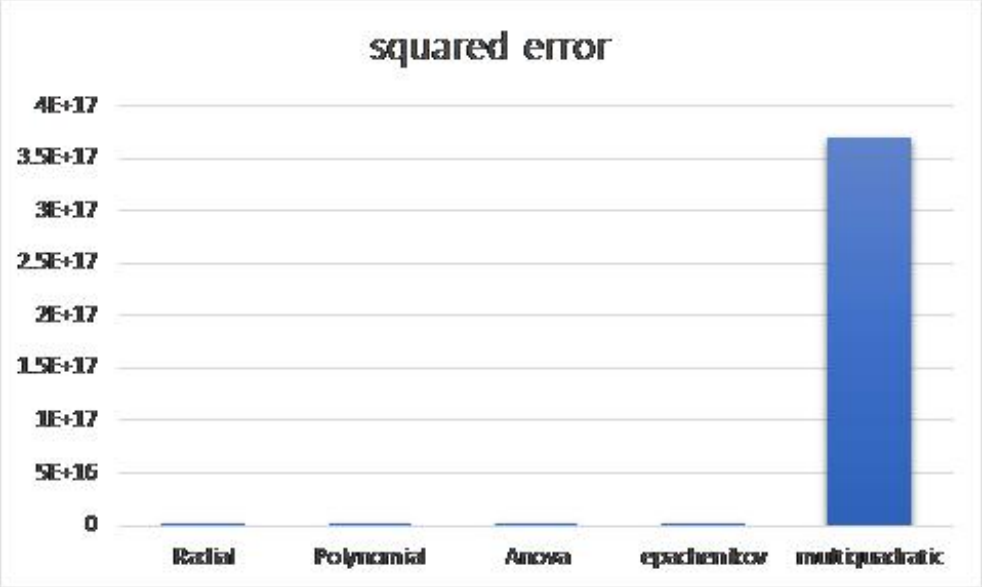

Figure 6.17: Results optimized squared error

With respect to the root mean squared error, the best improvements are obtained by Radial and Epachenenikov kernel functions with 95.86% and 95.93% respectively. For the mean absolute error metric the best improvements are obtained by the Radial and Epachenenikov kernel functions with 96.54% and 98.15% respectively. In the case of relative error lenient none of the values couldn't be improved. Finally, the

squared error is improved in the same measure for the Radial and Epachenenikov kernel functions with 99.86% respectively and 97.74% for the Anova. In summary the Epachenenikov kernel function has the best results.

Table 6.19 present the comparison between the results obtained by Deep Learning model with Boosting strategy and those obtained with Optimized Machine learning with the Epachenenikov Kernel function. In this case the optimized SVM with the Epachenenikov kernel function has the best results: the Root Mean Squared Error was reduced by 95.92%, the Mean Absolute Error was reduced by 98.04%, the Squared Error was reduced by 99.88% and the Relative Error Lenient was increased by 26.79%.

Performance measure	**D.L with boosting**	**Optimized SVM**	**% of improvement**
Root mean squared error	40716937.18	1663034.232	95.92%
Mean absolute error	11527546.61	225890.041	98.04%
Relative error lenient	0.6636	0.8414	-26.79%
Squared error	2.37334E+15	2.7657E+12	99.88%

Table 6.19: Comparison of D.L with boosting versus optimized machine learning with Epachenenikov kernel function

6.4 Analysis of the impact of comorbidity variables

In order to analyze the impact of the comorbidity in the performance of the machine learning models, two new variables were included: (i) the first variable is the Charlson Comorbidity Index which classify risks of patients based on comorbid conditions, the age and 19 different items that influence the expectation of life of patients [Charlson 1987]. Depending on some conditions there are five different levels or weights that is assigned to the patient, as follows:

- 1: for conditions of Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes.
- 2: for Hemiplegia, moderate or severe kidney disease, diabetes with end organ damage, tumor, leukemia, lymphoma.
- 3: for Moderate or severe liver disease.
- 0 to 5: depending on the age of patient
- 6: for Malignant tumor, metastasis, AIDS.

Each patient of the database was evaluated according to its condition and her/his Charlson comorbidity index was calculated and added to the database as a new variable.

(ii) the second variable is the number of comorbidities that each patient has been diagnosed, this variable was calculated and added to the data base as a new variable.

6.4.1 Machine learning models without boosting strategy

Tables 6.20, 6.21, 6.22, 6.23 and 6.24 present the results of the performance measures obtained by the machine learning models including the comorbidity variables.

Model	**Root Mean Squared Error**	**Standard Deviation**
Generalized Linear Model	866836.85	+/- 161222.39
Deep Learning	877670.34	+/- 160022.59
Random Forest	938964.41	+/- 157727.22
Gradient Boosted Trees	879746.02	+/- 160950.49
Support Vector Machine	887764.33	+/- 161890.62

Table 6.20: Root Mean Squared Error

Model	**Mean Absolute Error**	**Standard Deviation**
Generalized Linear Model	252715.60	+/- 34912.00
Deep Learning	268871.13	+/- 34000.41
Random Forest	275335.25	+/- 34595.75
Gradient Boosted Trees	258403.76	+/- 35460.47
Support Vector Machine	221611.18	+/- 36056.35

Table 6.21: Mean Absolute Error

Model	Relative Error Lenient	Standard Deviation
Generalized Linear Model	0.76	+/- 3.47%
Deep Learning	0.793	+/- 4.40%
Random Forest	0.752	+/- 1.58%
Gradient Boosted Trees	0.747	+/- 0.68%
Support Vector Machine	0.735	+/- 3.11%

Table 6.22: Relative Error Lenient

Model	Squared Error	Standard Deviation
Generalized Linear Model	2830820127962.64	+/- 627989064579.61
Deep Learning	2818872566790.44	+/- 624308728184.57
Random Forest	22871896908882.77	+/- 629520427438.99
Gradient Boosted Trees	2846349131840.61	+/- 630694996300.21
Support Vector Machine	2884802096633.26	+/- 637814743297.96

Table 6.23: Squared Error

Model	Correlation	Standard Deviation
Generalized Linear Model	0.258	+/- 0.066
Deep Learning	0.251	+/- 0.133
Random Forest	0.089	+- 0.145
Gradient Boosted Trees	0.207	+/- 0.206
Support Vector Machine	0.090	+/- 0.169

Table 6.24: Correlation

Given these results it can be concluded that there isn't an unique model that overperforms the others. In this case, the best result for the root mean squared error, mean absolute error and correlation is obtained by the generalized linear model. For the relative error the model with the best result is the support vector machine and for the squared error the best results is obtained by deep learning model.

As the generalized linear model is the one with the best results, table 6.25 presents the comparison of the results obtained by the Gradient Boosted Trees

model (without the comorbidity variables), model that obtained the best results in a first step of the first stage (see section 4.5.1) and those obtained by the generalized linear model (with comorbidity variables). In this case the best model is the generalized linear model (with comorbidity variables): the Root Mean Squared Error was reduced by 98.09%, the Mean Absolute Error was reduced by 98.37%, the Squared Error was reduced by 99.87%, the Relative Error Lenient was increased by 15.91%, and the Correlation was reduced by 56.20%.

Performance measure	**GBT without comorbidity**	**GLM with comorbidity**	**% of improvement**
Root mean squared error	45401130.757	866836.85	98.09%
Mean absolute error	15544911.101	252715.6	98.37%
Relative error lenient	0.6557	0.76	-15.91%
Squared error	2.11686E+15	2.8308E+12	99.87%
Correlation	0.589	0.258	-56.20%

Table 6.25: Comparison of gradient boosted trees without comorbidity with generalized linear model with comorbidity

6.4.2 Machine learning models with boosting strategy

With the comorbidity variables the boosting strategy is performed, the results are presented in Tables 6.26, 6.27, 6.28, 6.29 and 6.30.

Model	**Root Mean Squared Error**	**Standard Deviation**
Deep Learning	1655322.182	+/- 0.000
Random Forest	1655322.182	+/- 0.000
Gradient Boosted Trees	1655322.182	+/- 0.000
Support Vector Machine	1655322.182	+/- 0.000

Table 6.26: Root Mean Squared Error

Model	**Mean Absolute Error**	**Standard Deviation**
Deep Learning	269225.747	+/- 1633281.673
Random Forest	269225.747	+/- 1633281.673
Gradient Boosted Trees	269225.747	+/- 1633281.673
Support Vector Machine	269225.747	+/- 1633281.673

Table 6.27: Mean Absolute Error

Model	Relative Error Lenient	Standard Deviation
Deep Learning	0.7374	+/- 27.50%
Random Forest	0.7374	+/- 27.50%
Gradient Boosted Trees	0.7374	+/- 27.50%
Support Vector Machine	0.7374	+/- 27.50%

Table 6.28: Relative Error Lenient

Model	Squared Error	Standard Deviation
Deep Learning	2740091526194.531	+/- 32780320851464.027
Random Forest	2740091526194.531	+/- 32780320851464.027
Gradient Boosted Trees	2740091526194.531	+/- 32780320851464.027
Support Vector Machine	2740091526194.531	+/- 32780320851464.027

Table 6.29: Squared Error

Model	Correlation	Standard Deviation
Generalized Linear Model	0.21	+/- 0.12
Deep Learning	0.21	+/- 0.12
Random Forest	0.21	+/- 0.12
Gradient Boosted Trees	0.21	+/- 0.12
Support Vector Machine	0.21	+/- 0.12

Table 6.30: Correlation

As the results are similar for all models, in table 6.31 is presented the comparison between the deep learning model with boosting strategy (without comorbidity variables) and the models with boosting strategy (with comorbidity variables). The best results are related with models with boosting strategy (with comorbidity variables): the Root Mean Squared Error was reduced by 95.93%, the Mean Absolute Error was reduced by 97.66%, the Squared Error was reduced by 99.88%, the Relative Error Lenient was increased by 11.12%, and the correlation was reduced by 65.57%

Performance measure	D.L with boosting without comorbidity	D.L with Boosting with comorbidity	% of improvement
Root mean squared error	40716937.18	1655322.182	95.93%
Mean absolute error	11527546.61	269225.747	97.66%
Relative error lenient	0.6636	0.7374	-11.12%
Squared error	2.37334E+15	2.7401E+12	99.88%
Correlation	0.61	0.21	-65.57%

Table 6.31: Comparison of D.L boosting strategy without comorbidity with Boosting with comorbidity variables

The methodology used in this study shows a sequential decrease in prediction errors of the pharmaceutical expenditure. For example, the combination of DL with feature selection allows to reduce the mean error in absolute values from COP $ 15.544.911 to COP $ 12.227.186 then after implementing the boosting strategy this value were reduced to COP $ 11.527.546 Finally, with the addition of the comorbidity variables, this error was substantially reduced to COP $ 269.225 or COP $ 252.715 for the GLM model, which are reasonable prediction errors given the range of pharmaceutical expenditure analyzed and its mean that is around COP $ 18.657.000.

6.5 Conclusions

In this chapter is analyzed the use of machine learning models for predicting the pharmaceutical expenditure of a chronic disease as Diabetes by using an anonymized database of a hospital. In a first stage, different machine learning models were used and their performance indicators were analyzed. Some of these performances were improved trough the use of the feature selection method, nevertheless the variability were still high. For this reason, a boosting strategy was used combining the machine learning models with decision trees obtaining an improvement in the performance indicators and where the deep learning model obtained the best results. Also, an optimized support vector machines model was developed finding improvements in the prediction of the pharmaceutical expenditure. In a second stage, new variables of comorbidity such as the number of comorbidities and the Charlson index were calculated and added to the database, the experimentation was repeated by using the same models of the first stage. The results showed that the performance measures of some machine learning models were improved with and without boosting strategy, this leads to conclude that the inclusion of these comorbidity variables allows gaining better understanding and prediction of the pharmaceutical expenditure. In this way, the models used in this chapter can be used as a basis to estimate the pharmaceutical expenditure for illnesses classified as high cost for the health systems.

Chapter 7

Forecasting medicine consumption in seasonal epidemics using machine learning models

Contents

This chapter presents the application of two machine learning models combining the seasonal epidemics information and the consumption of medicines within hospitals. Two different models have been used: Neural Networks and Support Vector Machines in order to estimate the use of medicines in hospitals in the case of seasonal epidemics based on public database in Colombia. Different metrics to compare the performance of both models have been used.

7.1 Introduction

From the development of computers and mathematical models, applications of forecasting models in different hard sciences have been developed for trying to predict the future and therefore try to adapt to this circumstance. The main importance of forecasting is to support decision makers for planning, make decisions and formulate strategies in high and complex uncertainty environments [Hogarth 2009]. In this way, hospitals face a high uncertainty to planning its resources mainly because the increasing demand [Ivatts 2002]. Challenging decisions faced by hospitals cover

the providing of better healthcare service to patients such as admissions and medication care with several resource constraints and the minimization of the overall costs [Srikanth 2017].

Several factors can affect the health of people and therefore the demand of medicines and treatments in hospitals. There are studies that show that climate issues as air pollution, change of weather and others can affect the health of population increasing the admissions in hospitals [Sujit K. 2014]. There are also several variables that can affect the demand in hospitals as month, day of the week, holidays and many other factors. It is also proven that epidemic seasonality affect strongly the admissions in hospitals and the consumption of medicines [Chiumente 2017].

There is also an implicit importance of forecasting in the pharmaceutical supply chain process, it is the main step for managerial decisions in logistics and supply chain management becoming the starting point for any planning and execution process[Merkuryeva 2019].

The main objective of the pharmaceutical supply chain is to guarantee the access of medicines to patients. In this way is recognized that the correct estimation or modelization of the demand is a key factor for optimizing the supply of medicines. This becomes more critical in the case of seasonal epidemics due to the potential shortage of medicines required to guarantee the correct service level to patients. Additionally, forecasting medicines' consumption in seasonal epidemics could support the Colombian regulation (law 032 2016) related with the preparation of hospitals in seasonal epidemics. For this reason in this chapter, based on a public database, two different machine learning models: Neural Networks and Support Vector Machines are used to estimate the consumption of medicines in seasonal epidemics in Colombia.

7.2 Background

Several methods and approaches have been developed for estimating the use and consumption of different classes of medicines. [Wettermark 2010] present a linear regression model to estimate the sales of medicines in a hospital using a three years sales data in ambulatory care to build a statistical model that allows to predict two years of medicine consumption and expenditures.

A similar forecasting model was proposed by [Joppi 2015], the main idea of this work is to estimate the impact and the forecasting of new medicines and their impact in the national health system before they arrive into the national market. In a similar study presented by [Guseo 2017] a methodology for making pre-launch forecasting without explicit information about medicines is developed. By using diffusion dynamics of pre-existing medicines, authors introduce a methodology of

estimating a ranitidine demand in Italy.

An statistical analysis based on a Bayesian approach was developed in [Congdon 2006]. The main idea of this work is to estimate the health demand in regions with the objective of allocating resources. Main variables considered were: medical specialty, patients age and area of residence and then a gravity model is used. [Hou 2015] developed a Monte Carlo simulation, by using Crystal Ball, authors made an analysis of warehouse capacities for Beijing in 2020.

[Li Luo 2017] use ARIMA and Single Exponential Smoothing statistical models for predicting hospital daily outpatient visits. The model allows to predict one week of forecast and they consider 43 weeks of observation data obtaining as result that the combinatorial model achieve better predictions than single models with lower values of residual variance and mean of residual errors.

[Cheng 2016] use forecasting models for developing a method applicable in medical supplies for tertiary pediatric intensive care unit. The authors compare several methods finding that applying Croston's method combined with single smoothing exponential method allows to obtain better accuracy. Other application of ARIMA is presented in [Zhou 2018] where authors proposed a combination between ARIMA-Nonlinear Autoregressive Neural Network (NARNN) models for predicting the number of new admissions inpatients obtaining good accuracy results. Also, a classification method is developed for demand consumption allowing to minimize the forecasting errors. Another statistical application is presented in [Jones 2002] where authors consider the application in emergency care applying different methods and variables like illnesses, weather, seasonality and age, their method can obtain a forecast error of 3%.

On the other hand, Machine Learning and its methods have been applied in several applications to predict a different kind of issues in healthcare. For example in [Yangyang Ding 2018] authors develop a method for predicting mortality of patients in intensive care unit to prioritize resources and for helping doctors to make decisions. The main idea of the method proposed is to combine extreme machine learning method with just in time learning, the model is built with a set of 4000 real clinical records obtaining a better ROC-AUC index than those obtained in the literature.

As a main importance duty in emergency departments is classification of patients for emergency care, in [Krämer 2017] a machine learning approach for patients classification in emergency care using random forest trees and judgment of experts is developed. Also the readmission is studied with machine learning in [Shancheng Jiang 2018]. As re-hospitalization is the main source of cost of healthcare and because of capacity in hospitals is limited, authors develop a combined feature selection algorithms and machine learning approaches that allow to obtain

robust predictions over a different set of data.

Other application in healthcare is developed by [Mehmet Tan 2016] where a machine learning model for predicting drug activity on cancer cell lines is presented. The proposed model is partitioned into two stages: a preprocessing stage where a gene selection is proposed, and the second stage use a non-linear Kernel model. The proposed method is tested over three large datasets obtaining high performance results compared with previous results presented in the literature. Other study of effects of drugs in patients is studied in [Pierre Genevès 2018]. In this study authors develop a method to predict complication of patients during their stay in hospitals due to administration of different drugs.

7.3 Methods

The forecasting models developed in this chapter aim to predict the use of medicines in hospitals in the case of seasonal epidemics which are defined as the occurrence of a specific epidemic in a given population for short periods of time [ME 2018]. This is mainly motivated due to the fact that study consumptions of medicines in a more highly seasonal variation support the hospital's planning process and their understanding of the effects of seasonal epidemics over the consumption rates, this process could support the Colombian regulation 032/2016. To exemplify the problem addressed in this work, based on the analysis of the database used in this study the Figure 7.1 presents the consumption of one type of medicine over a two years horizon, in some periods of the year there are two types of seasonal epidemics expressed in the times of occurrence, it means a binary variable that takes the value of 1 if there is a seasonal epidemics and 0 otherwise.

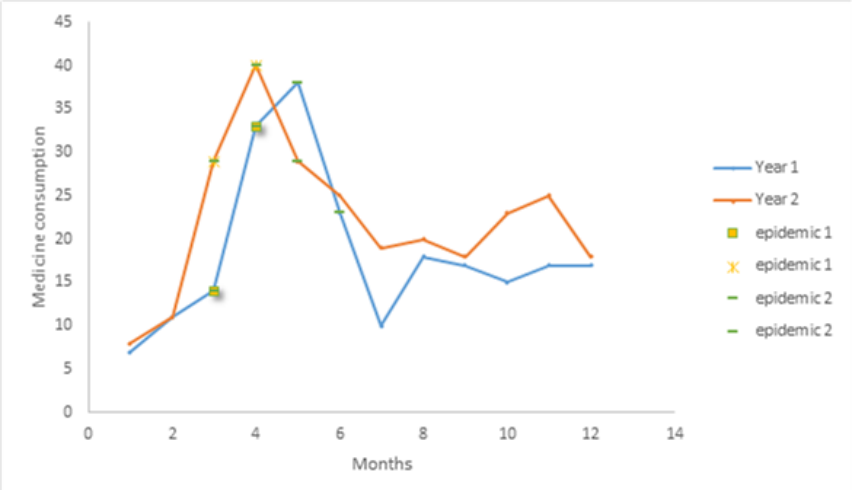

Figure 7.1: Demand of one type of medicine with two types of epidemics

Based on the public data base used in this study, in Figure 7.1 can be observed for one type of medicine that its consumption in the two years has a similar behavior, also it can be observed that when some epidemic (1 or 2 or both) is present in the time line (points with squares and/or lines) the consumption of medicines increases. Based on this context two strategies with machine learning in order to forecast the medicine consumption in seasonal epidemics has been used: Neural Networks and Support Vector Machines. The methodology used in this work is presented in Figure 7.2.

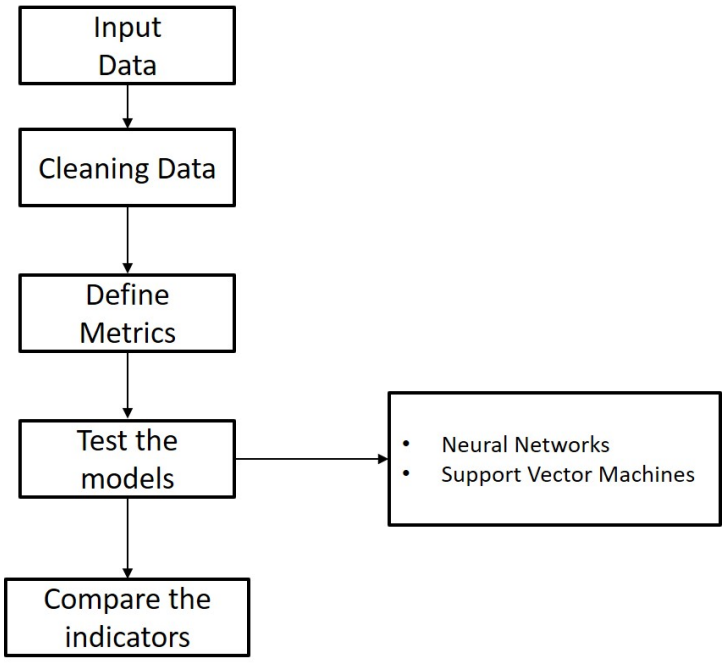

Figure 7.2: Methodology

7.3.1 Data description

In order to determine what is a seasonal epidemic or an epidemiological alert, the concept defined by the Ministry of health in Colombia was used, which is a public document that establish whenever a potential risk to the health of the population appears. This alert require the development of urgent and effective public health actions.

The information related with seasonal epidemics in Colombia is available in the website: https://www.minsalud.gov.co which contains a database of four different epidemics that are described as follows:

- Acute respiratory infection (ERA in Spanish): is a group of diseases that occur in the respiratory system caused by different microorganisms such as

viruses and bacteria. It starts suddenly and its occurrences are no longer than two weeks. It is the most frequent infection in the world and can produce a variety of illnesses like a simple cold but depending on the general state of the patient they can become in a pneumonia, otitis and/or sinusitis.

- Respiratory Syncytial Virus (VSR in Spanish): It is the virus that causes the highest amount of respiratory infections in children under 2 years, such as bronchiolitis or pneumonia, which are the most serious and can leave subsequent sequelae in a child's respiratory system, such as wheezing, recurrent respiratory diseases and alteration of lung function.

- Chikingunya: It is a viral disease that is spread by the bite of an specific infected mosquito, that is the same vector of dengue. It is characterized by a sudden outbreak of fever also with arthritis. Treatment focuses on relieving symptoms because there is no vaccine against the virus.

- Dengue: It is a viral disease that can affect people of any age, but children and older adults are more susceptible. It is caused by a virus transmitted through the bite of infected mosquitoes. Dengue mosquitoes lay their eggs in clean water tanks and any place that can store water.

The public database contains information related with two variables: First, the variables of medicine's type consumption in a hospital located in a specific region (the hospital treats patients coming from different regions and can treats different types of illnesses). The hospital provides a data set that specifies the medicines used in different years; specifically the quantity of four type of medicines (Acetaminofen + Codeina, Claritromicina, Dextrosa and Clemastina) used to satisfy the demand of patients. Second, the variable of seasonal epidemics, it was obtained by analyzing the reports generated by the minister of health related to the alerts of seasonal epidemics, more specifically the specific day-week-month that a specific epidemic is identified and the location where it occurs, as mentioned before information related with four type of epidemics were available (Acute respiratory infection, Respiratory Syncytial Virus, Chikingunya and Dengue). Based on this information, the consumption of medicines over two years were analyzed. The data base contains 2688 records of consumption of medicines, it means 672 records for each one of the types of medicines analyzed (1 record per day per medicine).

Variables

Table 7.1 present the description of the variables used is this study.

Variable	Description	Type
Type of epidemic	Type of epidemic considered	Binary
Period of occurrence	Period of time when seasonal epidemics	Binary
Demand of medicines	Demand of medicines	Integer
Duration of epidemic	Periods of time of the epidemics	Integer

Table 7.1: Description of variables

7.3.2 Data analysis

In order to contrast how the seasonal epidemics affects the consumption (in units) of medicines, boxplots that show the consumption with and without seasonal epidemics for each medicine were built, see Figures 7.3, 7.4, 7.5 and 7.6.

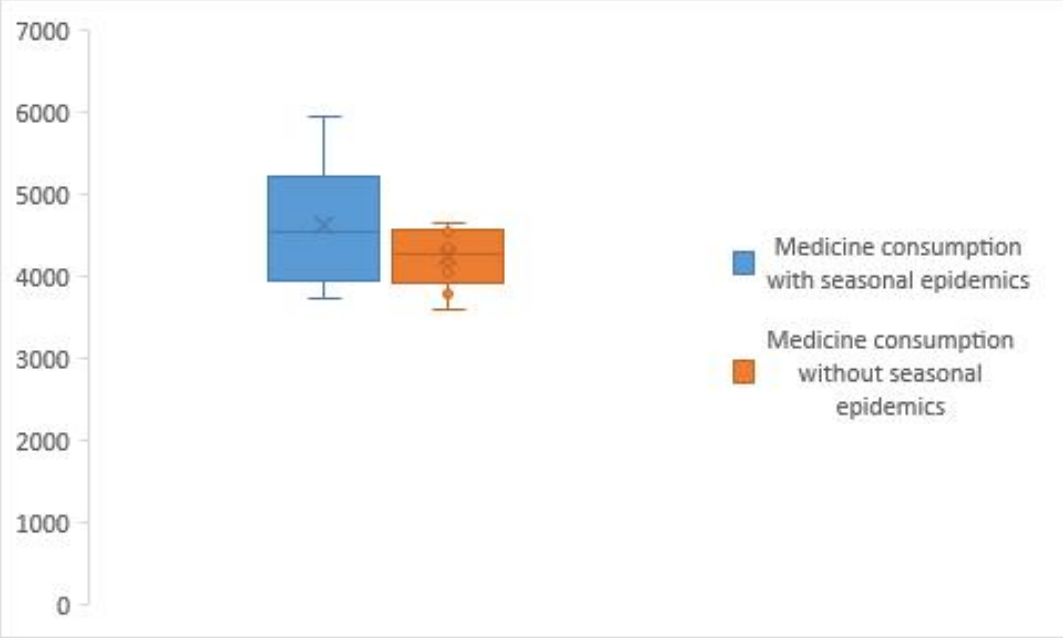

Figure 7.3: Boxplot of medicines consumption with and without seasonal epidemics for medicine 1

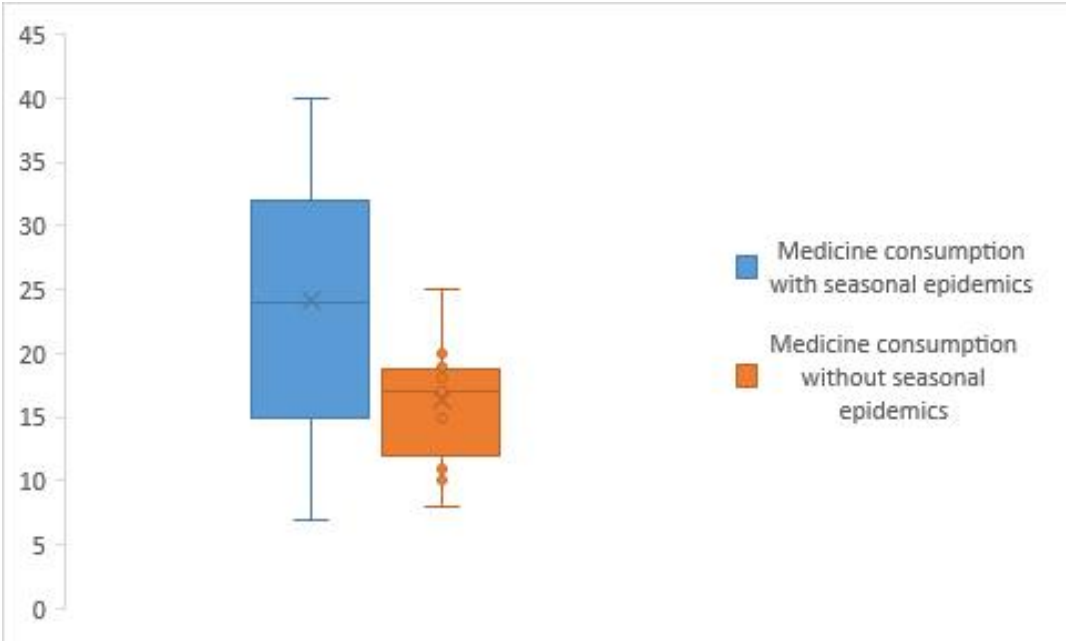

Figure 7.4: Boxplot of medicines consumption with and without seasonal epidemics for medicine 2

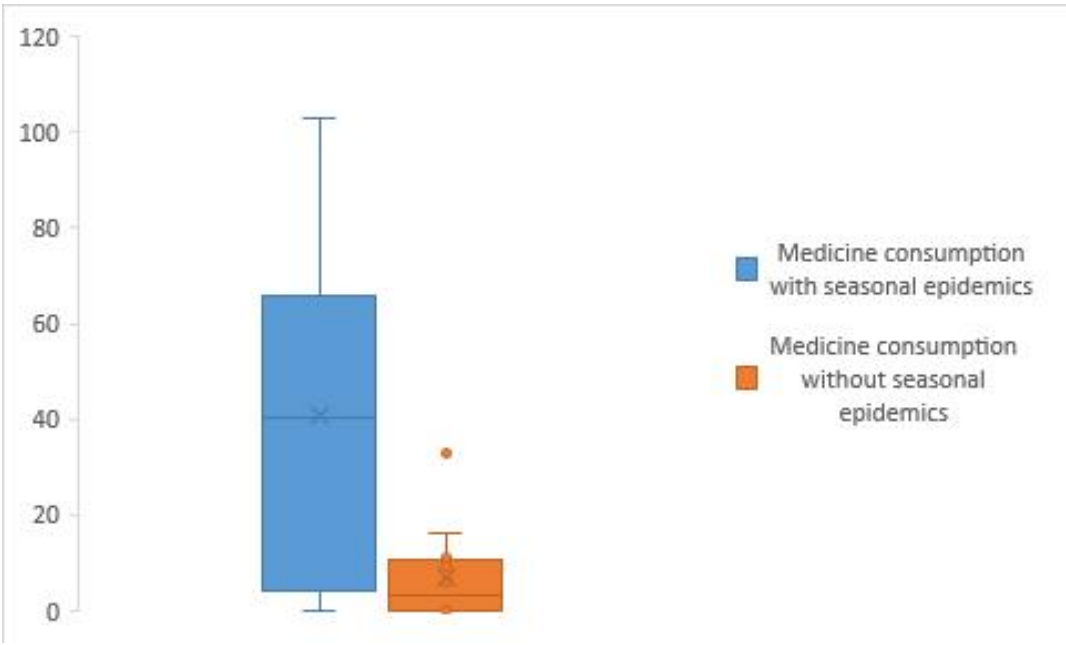

Figure 7.5: Boxplot of medicines consumption with and without seasonal epidemics for medicine 3

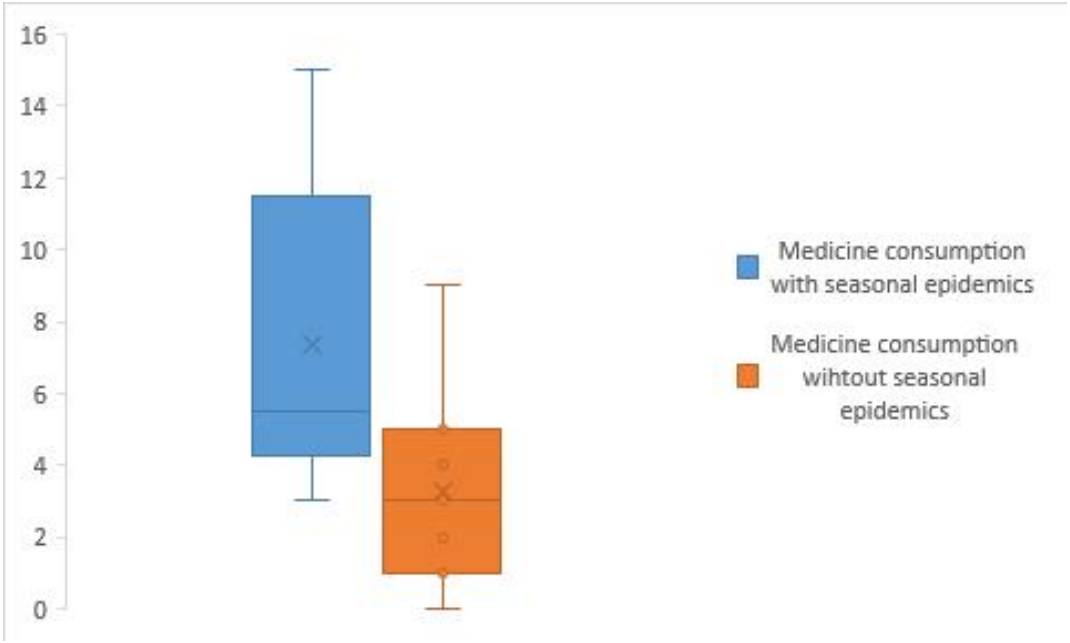

Figure 7.6: Boxplot of medicines consumption with and without seasonal epidemics for medicine 4

It can be observed that for the 4 medicines analyzed the consumption of medicines increases in seasonal epidemics epochs.

7.3.3 Neural networks

Neural Networks models are inspired in brain and its operation where the components refers to the neurons in the brain and the synapses between them [Stephen J. Read 2019], and the elements are nodes that represents neurons connected and the weighted links between them [Dreyfus 2005]. Other element of the neural networks is the hidden layers which transform the information of the inputs into information used to produce the output, the main idea of the Neural Networks is to make linear combinations of the inputs to fit nonlinear models to multidimensional data [Haykin 1994].

Based on this concept Figure 7.7 presents the representation of the proposed neural network that can be used to forecast the medicine consumption, where a single hidden layer is used.

The representation of the neural network proposed in Figure 7.7 is composed by neurons represented by the nodes and the arcs are the connections. The neural network is composed by three different layers (i) input layer, (ii) hidden layer and (iii) output layer. In the input layer the input variables related with the seasonal epidemic that affect the consumption of medicines are incorporated. The number

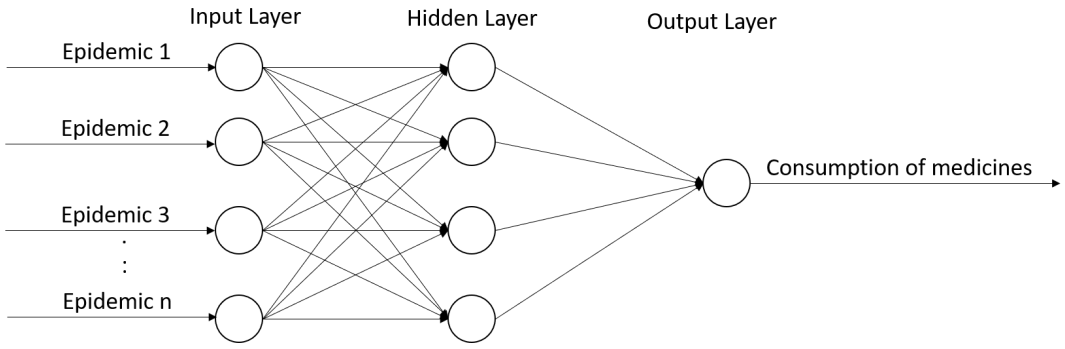

Figure 7.7: Neural Networks for demand of medicines prediction

of input variables depends of the number of epidemics and the number of epidemics that affect the consumption of medicines (correlational analysis). The hidden layer consists in a set of hidden unobserved variables or hidden units used to obtain the outcome [Kuhn 2013] that in this case corresponds to the consumption of medicines in a hospital.

The main general equation used in Neural Networks is as follows:

$$R(\theta) = \sum_{k=1}^{K} \sum_{i=1}^{N} (y_{ik} - f_k(x_i))^2 \tag{7.1}$$

Where y_{ik} corresponds to the observations weighted over each arc k and $f_k(x_i)$ corresponds to the regression coefficients of the hidden layers and connect the hidden layers to the outcome $R(\theta)$. In this case each one of the input layers represents an specific seasonal epidemics and y_{ik} is the weight of each one of these input layers (or epidemics) over each one of the hidden layers k which transom these coefficients to produce the output result $R(\theta)$ which is the medicine consumption prediction.

Also, to avoid the overfitting defined as the adjustment of a method closely or exactly to a particular set of data making difficult to use the model produced to forecasting or fitting over additional data, the equation is modified as:

$$R(\theta) + \lambda * J(\theta) \tag{7.2}$$

$$J(\theta) = \sum_{km} \beta_{km}^2 + \sum_{ml} \alpha_{ml}^2 \tag{7.3}$$

Where $\lambda \geq 0$ is the tuning parameter or the term of the regularization of the function and $\lambda * J(\theta)$ is the regularization function for avoiding overfitting which is composed by the squared sums of the loss function that is the sum of the weights of the components of the neural network.

7.3.4 Support vector machines

Support vector machines are a supervised learning algorithms focused on classification and nonlinear regression [Vapnik 2000], the main idea of support vector machines is to plot each data in a dimensional space and solve a mathematical model that maximize the margin between the samples and the separating hyperplane where the objective function is composed by the regularization, the classification error and the trade-off between them [Tang 2018]. Support vector machines uses a Kernel function to transform low dimensional input space into a higher dimensional space.

The Support Vector Machine with the objective of minimize use the following function (Equation 7.4):

$$W = C * \sum_{i=1}^{N} L(y_i, F(x_i)) + \sum_{j=1}^{P} B_j^2 \tag{7.4}$$

Where x_i corresponds to the inputs in this case the seasonal epidemics inputs, $L(.)$ is the loss function, B are the coefficients of the regularization term when considering P predictors (the predictors are associated with the seasonal epidemics inputs) and the constant C is the error penalty of the model. Also, the function $F(.)$ is a prediction equation for the demand of medicines that can be defined as follows (Equation 7.5):

$$F(x) = \sum_{i=1}^{N} \alpha_i * \varphi(x) + B_0 \tag{7.5}$$

Where α_i is the linear kernel function used to transform the input data to the required forms of relationships and B_0 a constant.

7.4 Performance measures

In order to avoid overfitting considered as the tendency of the machine learning and statistical models to fit the train sample extremely well, some data is used for training the algorithm, and the rest is used for testing its performance [Tea 2017]. Therefore, the data set used in this work is split 80% for the training sample and 20% for the testing sample.

To determine the effectiveness of the algorithms, the following accuracy measures has been calculated:

- Root Mean Squared Error (RMSE): is a measure of the differences between the predicted values of a model and the observed values that is considered as the standard deviation of the residuals. This measure is calculated as:

$$\frac{1}{n}\Sigma_{i=1}^{n}(y_i - f_i)^2$$

.

- Mean Absolute Error (MAE): is the average distance between each the observed value and the predicted value. This measure is calculated as:

$$\frac{1}{n}\Sigma_{i=1}^{n}|y_i - f_i|$$

.

- Gap: determines how close is the predicted value against the observed value. The average gap over the predicted values has been calculated as a percentage. This measure is calculated as:

$$\frac{1}{n}\Sigma_{i=1}^{n}\frac{y_i - f_i}{y_i}$$

Where n is the number of observations, y_i the observed value and f_i the predicted value.

7.5 Experimentation and results

Four different types of medicines have been selected and tested using the two different machine learning models: Neural Networks and support vector machines. Results are presented in Table 7.2. For each type of model and each type of medicine, the performance measures mentioned before are calculated.

Neural Networks						
Medicine	RMSE	MAE	Std Error	Mean	Mean Predicted	Gap
M1	483.99	425.43	80.10	4428.04	4412.07	-0.62%
M2	6.54	5.12	1.53	20.21	21.60	-13.95%
M3	28.93	22.54	5.33	23.83	26.43	-31.21%
M4	3.6	3.02	0.63	5.29	5.21	-21.09%
Support Vector Machines						
Medicine	RMSE	MAE	Std Error	Mean	Mean Predicted	Gap
M1	500.62	437.96	65.86	4428.04	4405.17	-0.60%
M2	6.54	5.12	1.55	20.21	19.96	-6.05%
M3	28.19	20.38	3.49	23.83	17.07	1.01%
M4	4.38	3.45	0.45	5.29	4.42	-23.72%

Table 7.2: Comparative performance of the machine learning models

From this results it can be concluded that for medicine 1 better results of RMSE and MAE are obtained by the neural network model nevertheless the standard error and the gap are performed better by the support vector machines algorithm, also the mean of the predicted values performs better on the Neural Networks with 0.36% of gap. In both models for medicine 1 the average gap underestimate the predicted values with -0.62% and -0.60 respectively. For medicine 2 results of RMSE and MAE

are equal from both models (Neural Networks and support vector machines), the standard error presents a lower value in the Neural Networks model but with a little difference between them -1.53 versus 1.55- for the mean predicted and gap there are differences between the results of both models and the best performance is obtained by the support vector machines model with and underestimated gap with -6.05% over and overestimated gap of 13.95% generated by the Neural Networks, also the mean predicted is closer in support vector machines with -1.24% versus 6.88%.

For medicine 3 results show that except for the mean predicted, the results obtained for the support vector machines model improve those obtained by the Neural Networks model, in fact the gap is within 1.01% in SVM while in Neural Networks is -31.01%. In the case of the mean predicted, Neural Networks results are 10.91% closer to the real mean compared with -28.37% obtained by the SVM algorithm. Finally, for medicine 4, RMSE, MAE, mean predicted and the gap presents lower values in the results of the Neural Networks, while the standard error presents a lower value in the SVM model.

In order to compare the results provided by the Neural Networks and support vector machine (SVM) models, box-plots of real data and predicted values of each medicine are presented in Figures 7.8, 7.9, 7.10 and 7.11 for medicines 1, 2, 3 and 4 respectively. It is clear that for medicines 1, 2 and 3 the mean obtained by SVM is closer to the mean of the real data, for medicine 4 the mean obtained by the Neural Network model is closer to the real data.

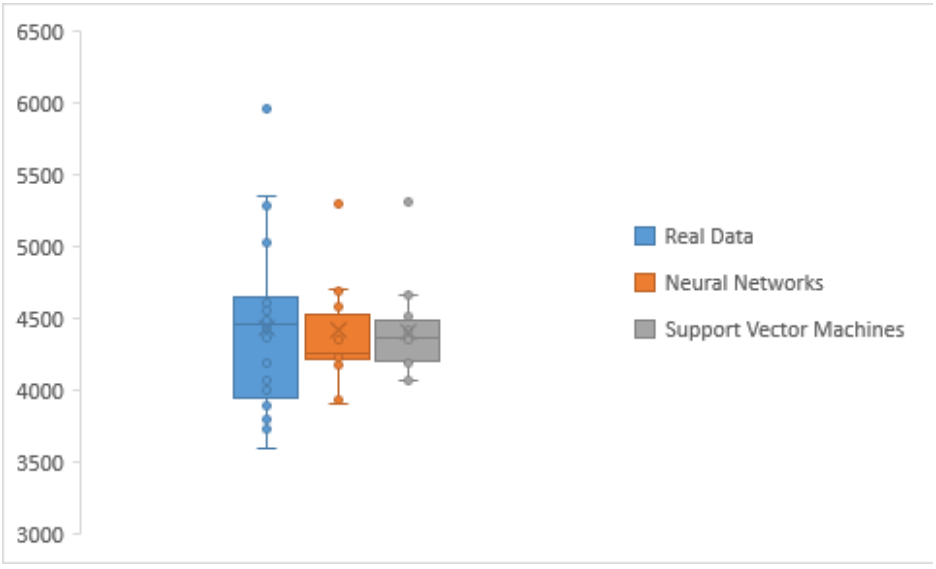

Figure 7.8: Boxplots of real data and predicted values for Neural Networks and SVM for medicine 1

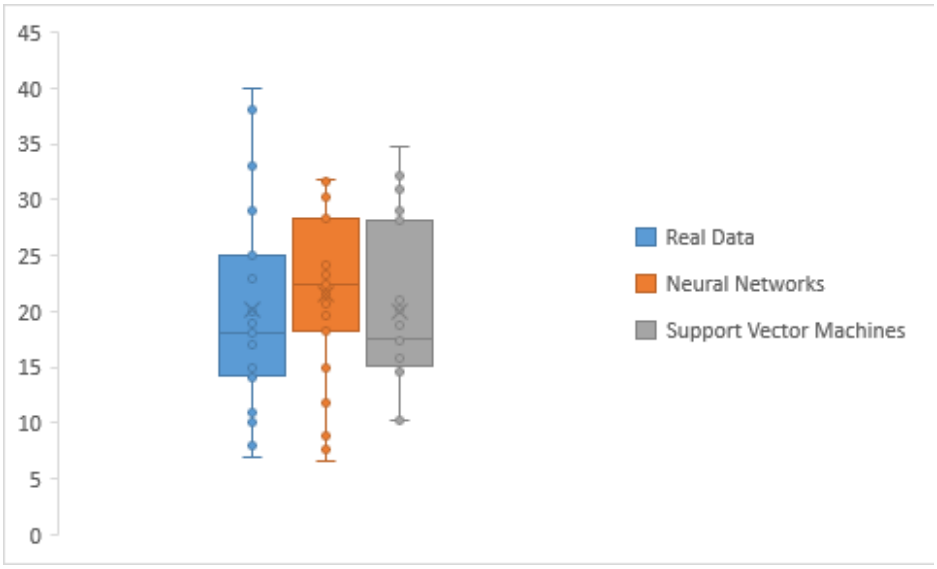

Figure 7.9: Boxplots of real data and predicted values for Neural Networks and SVM for medicine 2

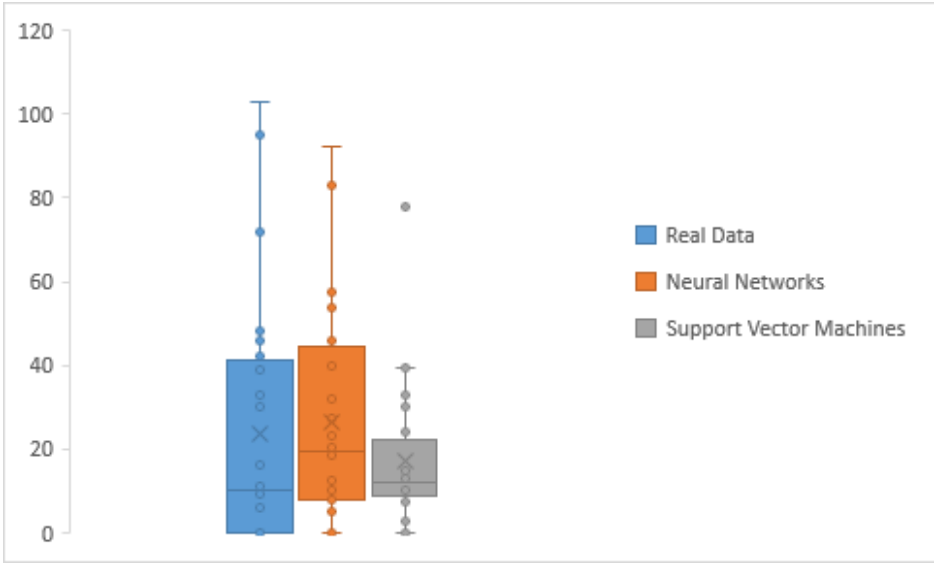

Figure 7.10: Boxplots of real data and predicted values for Neural Networks and SVM for medicine 3

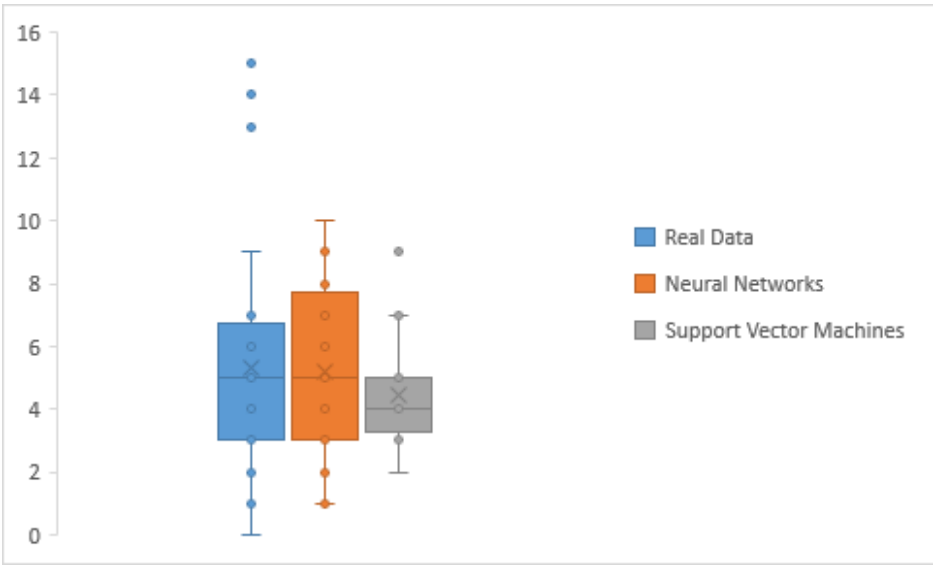

Figure 7.11: Boxplots of real data and predicted values for Neural Networks and SVM for medicine 4

Finally, Figures 7.12, 7.13, 7.14 and 7.15 present the comparison of the estimation over time of Neural Networks and SVM models for medicines 1, 2, 3 and 4 respectively. It can be concluded that results for both models generates under and over estimation of the consumption of medicines. Graphically it seems that Neural Networks capture better the epidemiological peaks than the SVM model however both models capture the seasonal behavior.

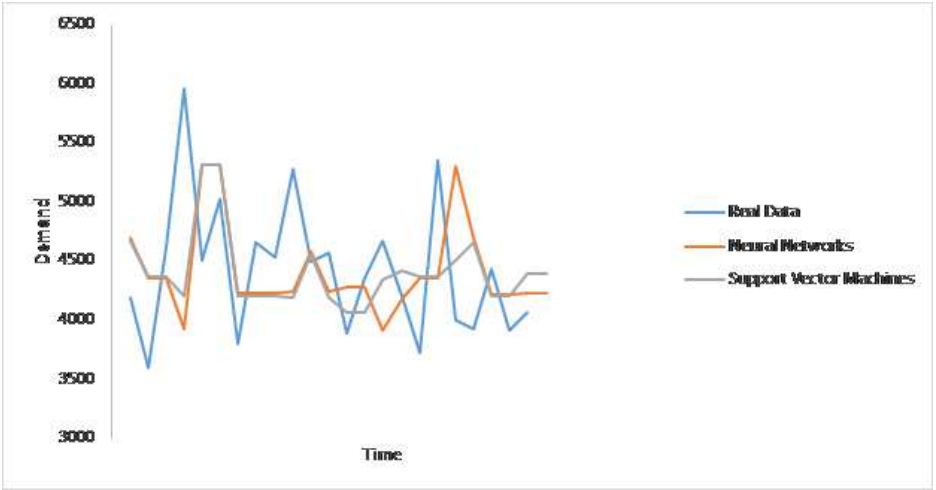

Figure 7.12: Estimations produced by machine learning models for medicine 1

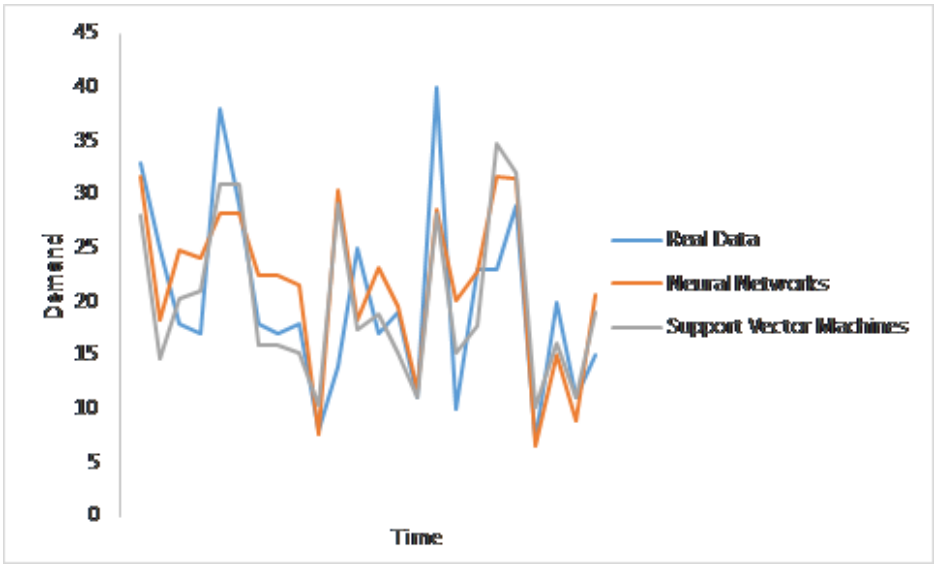

Figure 7.13: Estimations produced by machine learning models for medicine 2

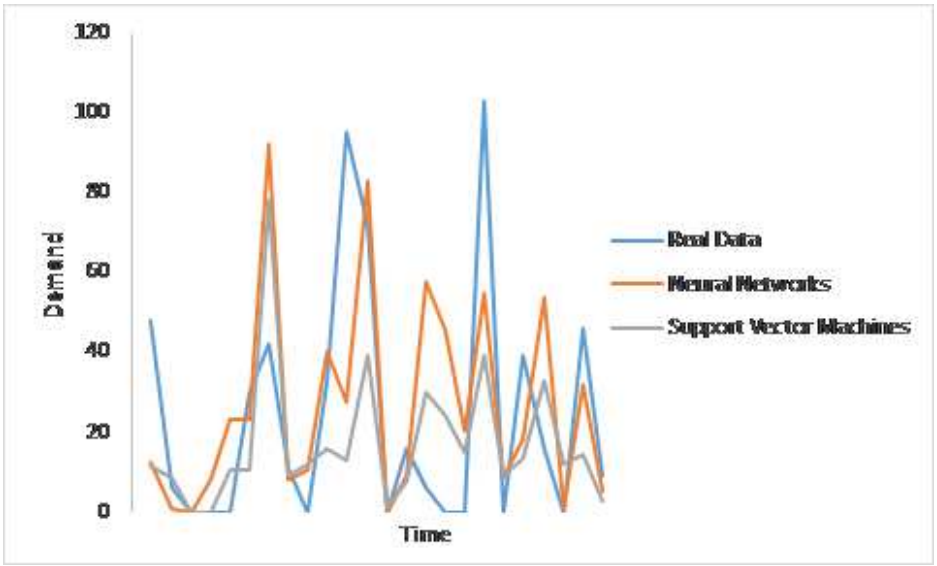

Figure 7.14: Estimations produced by machine learning models for medicine 3

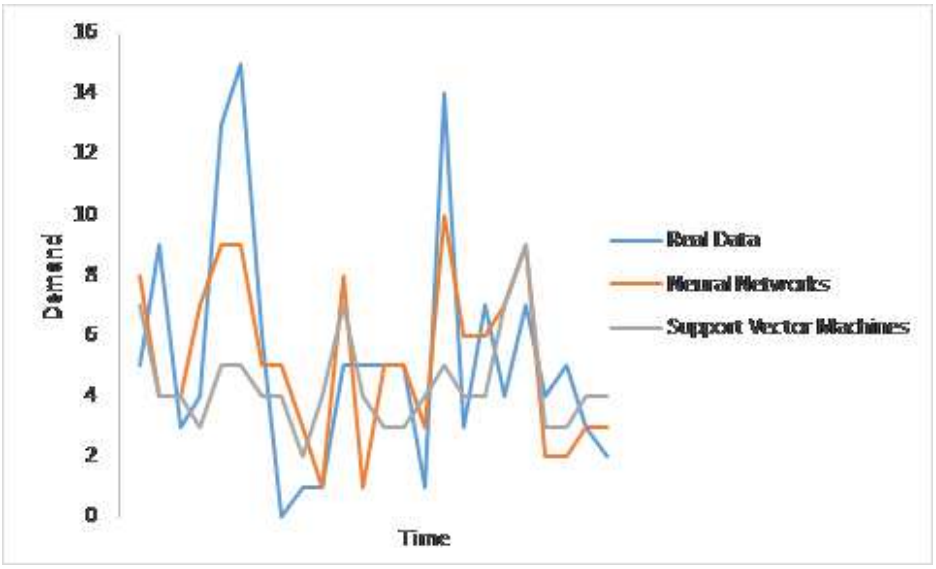

Figure 7.15: Estimations produced by machine learning models for medicine 4

The Machine Learning models used in this study to predict medicines' demand in seasonal epidemics work reasonable well with medicines with high consumption values, for example for the medicine 1 which has the highest demand, the mean error in absolute values is 425.43 units using Neural Networks and 437.96 using Support Vector Machines, which are reasonable prediction errors given the range of medicine consumption and its mean that is around 4428.04 units for the seasonal epidemics analyzed. However, for medicines with low consumption values, the prediction errors are high.

7.6 Conclusions

In this chapter, supervised machine learning models have been used to estimate the consumption of medicines within hospitals, more specifically Neural Networks and Support Vector Machines. For the learning process the seasonal epidemics and the consumption of medicines in hospitals obtained by a specific hospital data and public data alerts of seasonal epidemics has been used.

Different metrics for comparing the performance of both models have been used: root mean squared error, mean absolute error, mean predicted and the gap, also the graphics for comparing predicted values and the real values are presented. It can be found similarities in the performances of both models where both are useful for predicting the consumptions of medicines, in some metrics the neural network obtain better results than support vector machines but this not occurs over all metrics.

In conclusion, even that estimation of consumption of medicines within hospitals is a complex and challenging task, machine learning models considering seasonal epidemics enhance prediction accuracy of the demand of medicines within hospitals.

A direction of future research will include other type of factors that not only consider the seasonal epidemics and therefore could help to improve the forecasting process in non-epidemic seasons. This will introduce the use of new type of data such as: patients profiles (age, gender,...), weather, among others.

Chapter 8

Conclusions

In this thesis different problems associated with pharmaceutical supply chain, making emphasis in the hospital's echelon, have been addressed using different methodologies of operational research, simulation and machine learning approaches which allow an appropriate representation of the real situation under study and to support the process of decision making in this context.

In this way, in chapter 3 through a conceptual modeling framework of the pharmaceutical supply chain in hospitals by using causal loop diagrams and a simulation model based on system dynamics was possible to understand the behavior of supplying medicines to patients and the behavior of the pharmaceutical costs in hospitals, enabling to contrast the reimbursement value regulated by governmental policies with the costs associated with the logistic process of medicines administration in the hospital. In the same sense there are some illnesses that must be treated as special due to its complexity of treatments and the high costs that represents to the health system, for this reason, in chapter 6 machine learning approaches and combined methods were used to predict the pharmaceutical expenditure in a specific case of a chronic disease (diabetes). In this analysis the impact of the comorbidity in the performance of the machine learning models to estimate the pharmaceutical expenditure was analyzed. These models can be used as a basis to evaluate the governmental policies in terms of reimbursement prices of medicines and the particular conditions of the hospitals helping the managers of health systems to support decisions in the managing of medicines.

From tactical and operational point of view, in Chapter 4 mathematical models based on a simulation-optimization approach were developed as decision tools to coordinate logistic decisions of medicines supply in hospitals taking into account the sources of uncertainty and other elements related with legal regulations. The optimal policies obtained by these models could improve the managing of medicines by reducing the total logistic costs and help to define policies for negotiation with medicine suppliers in terms of the medicines expiration dates, emergency purchases prices and lead times, in order to reduce the operational costs.

From a strategic point of view, in Chapter 5 deterministic and stochastic optimization approaches were used to determine configurations of location-allocation of pharmaceutical robots in a network of hospitals considering constraints related with the operation of preparing and distributing unit-doses and prescriptions, tak-

ing into account the uncertainty of the demand of medicines and the multi-source resilience strategy to avoid the risk of centralized distribution processes of medicines and prescriptions. These models can support strategical and operational decisions in a context of coordination and collaboration between hospitals with the purpose to guarantee an adequate service level to the patient and to and improve the efficiency of the system.

Finally, in Chapter 7 machine learning models are used to estimate the use of medicines in hospitals in the case of seasonal epidemics, by using the data related with medicine's type consumption in hospitals of public databases in Colombia and epidemiological alerts. These models can help decision makers to manage the uncertainty associated to the consumption of medicines in a high variable seasonal epidemic, allowing a better planning of supply of medicines and management of budget.

Perspectives

Future perspectives of research are related with the inclusion and analysis of different information of some of the echelons of the pharmaceutical supply chain, for example economic factors and policies related with pharmaceutical companies or distribution of medicines in a global market, to determine their impact in the chain and thus on the health system and establish strategies of collaboration and coordination between the echelons of the chain and coordination with governmental agencies in order to generate strategies and policies for sustainable health systems in terms of costs, coverage and quality of care for people and economical benefits for the echelons of the chain.

On the other hand, it could be interesting to characterize and optimize the pharmaceutical supply process of high costs medicines and/or those with special features such as oncological medicines or personalized medicines.

Research about the development of methods to combine machine learning and optimization approaches in order to find optimal solutions in a context of uncertainty with a high volume of data. In this way, for example the study of generic medicines, their effectiveness on patient health, and their impact in the total cost could be analyzed.

Finally, an analysis of the impact of new information and communication technologies and new logistic strategies in the pharmaceutical chain can be developed.

Appendix A

Appendix

Medicine-Supplier	P-Values - Lead Times	P-Values - Costs
Medicine 1-Supplier 1	0.567	0.232
Medicine 1-Supplier 2	0.742	0.444
Medicine 2-Supplier 2	0.281	0.074
Medicine 2-Supplier 1	0.673	0.577
Medicine 3-Supplier 2	0.0373	0.685
Medicine 4-Supplier 3	0.0616	0.191
Medicine 5-Supplier 4	0.0486	0.462
Medicine 6-Supplier 4	0.0651	0.15
Medicine 7-Supplier 4	0.0792	0.149
Medicine 8-Supplier 4	0.0872	0.62
Medicine 9-Supplier 5	0.712	0.232
Medicine 10-Supplier 6	0.752	0.737
Medicine 11-Supplier 1	0.008	>0.75
Medicine 12-Supplier 2	0.0925	0.0935
Medicine 13-Supplier 2	0.0458	0.38
Medicine 14-Supplier 2	>0.005	0.0643
Medicine 15-Supplier 7	0.0347	0.232
Medicine 16-Supplier 8	>0.005	0.678
Medicine 17-Supplier 9	0.0478	0.678
Medicine 18-Supplier 1	0.0243	0.38
Medicine 19-Supplier 1	0.0153	0.0166
Medicine 20-Supplier 10	0.345	0.128
Medicine 21-Supplier 1	0.0768	0.504
Medicine 22-Supplier 2	0.0777	0.678
Medicine 18-Supplier 2	0.157	0.0272
Medicine 19-Supplier 2	0.006	0.232
Medicine 21-Supplier 2	0.0188	0.0838
Medicine 22-Supplier 1	0.0229	0.0643

Table A.1: Chi Square test results lead times and cost of medicines

Medicine	P-Value Mann-Kendall test	Z value Laplace test
Medicine 1	9.03E-12	10.02
Medicine 2	4.22E-11	3.49
Medicine 3	8.83E-11	2.07
Medicine 4	3.13E-11	2.04
Medicine 5	1.98E-11	-2.02
Medicine 6	1.06E-11	16.87
Medicine 7	1.06E-11	13.16
Medicine 8	1.45E-11	11.20
Medicine 9	1.69E-11	1.99
Medicine 10	2.29E-11	4.14
Medicine 11	8.36E-11	-10.08
Medicine 12	5.58E-11	-3.07
Medicine 13	8.99E-11	-29.99
Medicine 14	1.98E-11	4.57
Medicine 15	1.43E-11	-17.74
Medicine 16	1.34E-10	5.77
Medicine 17	1.06E-11	7.67
Medicine 18	9.03E-12	18.80
Medicine 19	1.45E-11	5.36
Medicine 20	1.24E-11	3.50
Medicine 21	1.68E-11	2.25
Medicine 22	9.03E-12	9.34

Table A.2: Mann-Kendall and Laplace tests results

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