Stochastic Optimization and Game Theoretic Approaches for Healthcare Supply Chain Analytics

A Dissertation

Presented to

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in Industrial Engineering

by

Samira Saedi

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Stochastic Optimization and Game Theoretic Approaches for Healthcare Supply Chain Analytics

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To my parents

Farzaneh Salahchin & Hosseinali Saedi

with all my love

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Abstract

Reduction in the availability of healthcare due to limited financial resources from one end and an aging U.S. population from the other end necessitate effective use of resources in the health sector. This dissertation, addresses two applications of maximizing the quality of health service, namely, (i) diabetic foot ulcer prevention, and (ii) mitigating the impact of national pharmaceutical shortages.

The first study deals with assessing the effectiveness of education and timely treatment to prevent diabetic foot ulcers and consequences. Considering the increasing population of diabetic patients, the lower quality of life in patients with foot ulcers, and higher treatment costs for diabetic patients with foot ulcers requires effective prevention strategies and timely treatment. In this study, a decision support system is proposed to evaluate cost-effectiveness for prevention strategies and receiving timely treatment. The anticipated outcome from this study is not only finding the effect of prevention strategies and timely treatment for different types of patients, but also an optimal threshold for expenditures on prevention strategies and treatments.

In the second study, two different analytical approaches to solve the drug shortage problem are investigated. Despite the importance and value of the pharmaceutical market, a significant portion of public procurement spending is known to be lost due to poor practices such as inefficient management of orders and inventory. Together with the inevitable national drug shortages, inefficient inventory management causes lack of medicine leading to patients suffering and has direct life or death consequences.

In this research, two different approaches are proposed to reduce critical shortages of healthcare providers. In the first approach, the optimal inventory policy for a healthcare facility is studied that minimizes the effect of drug shortages in the presence of uncertain supply disruptions and uncertain demand. Computational studies show

significant cost savings for the proposed solution compared to the current inventory policy for a local healthcare facility. Second, an inventory sharing scheme is proposed, where hospital decisions are to be studied in a game theory setting. This study is expected to mitigate the impact of shortages for sets of facilities that can collaborate in an inventory sharing scheme without logistics issues.

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Chapter 1

Introduction

According to the World Health Organization (WHO) (2009), the United States has the highest spending on health in the world with 16.2% of its GDP in 2009 and this amount is expected to grow. The aging U.S. population and limited financial resources mandate improvements to efficient use of healthcare resources. In this portion of the dissertation, two main problems in healthcare services are introduced. In Section 1, a brief introduction about diabetic foot ulcers and the necessity of timely treatment and primary preventive strategies are presented. Section 1.2, introduces another major problem in the health sector, national drug shortages. In this section, the importance of drug shortages is explained and two possible approaches to help healthcare providers to face this problem are introduced.

1.1 Cost-effectiveness Analysis for Diabetic Foot Ulcers (DFU): Timely Treatment and Primary Prevention Strategies

The quality of life in diabetic patients is highly affected by microvascular, macrovascular, and neuropathic complications. Foot ulceration is one of the main health issues of diabetic patients and can cause lower-limb amputation in patients. More than half of lower-limb amputations in the U.S. occur in diabetic patients (Reiber et al., 1995). DFUs are associated with depression, anxiety, guilt, fear and loss of perceived control (Ribu and Wahl, 2004). Foot ulceration does not only result in a lower quality of life, but healing is costly. Treatment of foot ulcers needs expert interference, orthopaedic appliances and antimicrobial drugs as well as costly topical dressings and inpatient care (see e.g., (Boulton et al., 2004); (Cavanagh et al., 2005); (Edmonds and Foster, 2006); (Jeffcoate and Harding, 2003); (Singh et al., 2005)). According to Cavanagh et al. (2012), the healing of ulcers costs approximately

between $\$3,959$ - $\$188,645$ based on the severity of the ulcer.

According to Boyle et al. (2010) the annual diagnosed diabetes incidences (new cases) will increase from about 0.8% in 2008 to about 1.5% in 2050. Considering low incidence and relatively high diabetes mortality, total diabetes prevalence, diagnosed and undiagnosed patients, will increase from 14% in 2010 to 21% of the U.S. adult population by 2050 while if incidence rate increases with current speed and diabetes mortality is low, prevalence will increase to 33% by 2050. The prevalence rate of foot ulceration among diabetic patients ranges from 1.3% to 4.8% in the community, to as high as 12% in hospitals (Boulton et al., 2005). However, the lifetime risk for any diabetic patient is up to 15% (Reiber et al., 1998) and 70% of healed foot ulcers recur within 5 years (Apelqvist et al., 1993). In 2007, diabetes cost the United States more than $174 billion per year, of that $116 billion were in direct costs and $58.3 billion in indirect costs such as loss of productivity, disability, and premature mortality. Thirty one percent of these expenses were associated with peripheral vascular complications and 24% with neurologic complications, and they were among the major reasons of prolonging the inpatient length of stay (Association, 2008). Therefore prevention strategies for diabetic foot ulcers is an increasingly important issue.

Resource allocation should be done more systematically in healthcare because of limited healthcare resources and the unsustainable rate of growth of U.S. health care costs and its impact on the overall U.S. economy. In light of the rising prevalence of diabetes all over the world and limited heathcare resources, the cost-effectiveness study of diabetic foot ulcer prevention strategies and timely treatment is crucial for the U.S. healthcare system. In the study introduced in Chapter 2, cost-effectiveness of timely treatment and primary prevention strategies on diabetic foot ulceration is presented.

1.2 Pharmaceutical Supply Chain Analytics

A shortage in healthcare supply chain occurs when a biological product is not commercially available in sufficient quantity to meet patient demand (Food and Administration, 2010). According to the World Health Organization (WHO), the United States has the

highest expenditure on health in the world with $750 billion spent in the global pharmaceuticals market (Boerma et al., 2009). The United States pharmaceutical market itself is valued at more than $306 billion (US Pharmacy), with an annual growth of approximately 5%. However, 10% to 25% of public procurement spending (including pharmaceuticals) is lost due to inefficient practices. This leads to shortages and inefficiencies in the delivery of critical healthcare supplies through the existing pharmaceutical supply chain. In light of these inefficiencies, Landry and Philippe (2004) estimate that 48% of the costs in the pharmaceutical supply chain are avoidable. Of these costs, 41% are sustained by healthcare providers, 33% by the manufacturers, and 26% by the distributors. Since much of the healthcare provider cost is passed along to patients, we believe that there are clear opportunities to improve the management of pharmaceuticals to eliminate wasted costs and improve service to patients.

In addition to the financial implications stemming from inefficient pharmaceutical management, there are shortages that result from these poor practices. A total of 1190 shortages were reported between January 2001 and June 2011. However, from 2006 onwards the shortages grew annually by 200 percent. A record number of shortages (196) were reported in 2010, and 2011 in all likelihood surpassed this number (General Accountability Office (GAO), 2012). Drug shortages can cause delay in treatment, inappropriate treatment, medication errors and thus increase in healthcare resource utilization and expenditures. The Food and Drug Administration (FDA) has been involved in addressing the problem of drug shortages. However, despite the fact that it has helped alleviate some of the shortages through its Drug Shortage Program, its authority to regulate the manufacturers is limited. There is no mechanism available to the FDA that require the drug manufacturers to report impending shortages or require them to take certain actions to avert the situation leading to shortages (General Accountability Office (GAO), 2012). On October 31, 2011, the President issued an Executive Order in which he urged the congress to legislate requiring drug companies to report shortages. The executive order directed the FDA to take action to help further prevent and reduce prescription drug shortages (The White House, 2011). Consequently, a drug shortage bill was introduced in January 2012 in the House of

Representatives that would force the FDA to speed up its review of applications from the companies that want to ramp up production to meet the shortages.

The drug shortage problem is a complex phenomenon and stems from legal, regulatory, economic and clinical factors. There are a number of contributing factors towards creating drug shortages. A key contributor to the shortage problems are manufacturers' business decisions in response to economic environment and incentives to earn profits or mitigate losses (Fox and Tyler, 2003). This is particularly true of the generic market which has a major share of the drugs that are in short supply. The generic market typically is very competitive and thus has low profit margins, which makes it critical for the manufacturers in the generic industry to constantly allocate and reallocate manufacturing resources and to deploy existing production capacity among products on the basis of conjectures regarding their competitors. The generic market further underwent major transformation in the wake of a series of patent expirations since 2008, in particular chemotherapy drugs, making the problem of shortage worse since it takes several years for the new firms to enter establish necessary capacity (Office of Science and Data Policy, 2011).

A survey of 353 pharmacy directors in the United States hospitals conducted by American Society of Health-Systems Pharmacists in 2011 revealed that the yearly labor costs to manage drug shortage problems amounted to $216 million nationwide (Kaakeh et al., 2011). Another 2011 survey of 820 U.S. hospital, completed by the American Hospital Association, showed that the surveyed hospitals experienced at least one shortage in the past 6 months. Another survey of 1800 health practitioners, of which 68% were pharmacists, was conducted by the Institute for Safe Medication Practices in 2010. The results of the survey revealed that the most of those surveyed encountered shortage problems and that they managed the problems by using less effective and/or more costly alternatives with an increased potential for medication errors and worse patient health outcomes.

Failures in the pharmaceutical drug supply chain, which includes hospitals and outpatient clinics, pose a direct threat to the quality of care received by a patient in the United States. Shortages result in patient treatment times being prolonged or procedures (e.g., surgeries) being canceled. Specific medical examples of critical shortages are readily

available (Landis, 2002). The following are only a subset of those reported:

- *10-fold overdoses of epinephrine (adrenaline) have been reported as a result of staff using an undiluted form of the drug when pre-diluted syringes were unavailable.*
- *The unavailability of succinylcholine, a rapid-acting neuromuscular, threatens hospital abilities to position airway tubes in emergency patients.*
- *Patients with hypertension are at risk in surgery due to the unavailability of ephedria.*

The severe consequences and logistic challenges resulting from ineffective pharmaceutical drug supply chain practices leave hospitals frustrated (Landis, 2002).

In the case that a hospital experiences a drug shortage, several courses of action have historically been performed. Hospitals often choose from borrowing from another institution (e.g., hospital or pharmacy), purchasing off-contract from their current vendor, purchasing from an alternative vendor, purchasing from a secondary vendor, obtaining services from a secondary group purchasing organization (GPO), purchasing a compounded replacement pharmaceutical and using a compound replacement pharmaceutical already in stock (Baumer et al., 2004). Frustration regarding shortages have been voiced for the last decade, with key players (e.g., manufacturers and healthcare providers) willing to discuss the issue from varying perspectives (Landis, 2002). From the discussions amongst practicing professionals, the following key issues have been raised: (i) limitations of federal regulatory to require manufacturers to make certain drugs, (ii) increased risk of drug shortages due to single supplier model and (iii) generic drug product subject to commodity business models. Solutions to these problems have been brainstormed by the key players. Many of these suggestions offer new qualitative measures to consider. For example, they suggested: (i) better communication between the FDA, manufacturers and pharmaceutical customers; (ii) reporting tools for drug shortages and (iii) increased inspections of manufacturing facilities to reduce possible production delays. While these solutions merit additional considerations, they are focused more on managerial oversights than improved operational planning. However, the decision makers have also identified tactics that could be evaluated and improved through analytical planning techniques. Specifically, we find the following solutions warrant

thorough quantitative exploration:

- **Refined hospital inventory policies**. The coalition cited inventory policy at both the manufacturer and healthcare provider levels to be in need of improvement. Specific suggestions include the rationing of inventory, as well as the establishment of new reorder points in the inventory management system.
- **Hospital collaboration through inventory sharing**. Opportunities exist to make use of collaborative inventory agreements that are more standard in retail logistics. These agreements would make way for portions of individual hospital inventory to be shared amongst participating hospitals. Policies that ensure the equitable distribution of inventory costs and supply amongst partnering healthcare facilities could lead to a drastically reduced number of shortages. These types of institutional collaborations are quite common in healthcare industry for epidemic control in the form of shared services.

Motivated by input from contributors to the pharmaceutical supply chain, our proposed research suggests mathematical models and analysis to intelligently evaluate each of the preceding options. Our work will be divided into two categories: (i) single hospital critical inventory analysis and (ii) exploration of collaborative hospital inventory sharing. The structure of the single hospital inventory problem is explained in more details in Chapter 3. In this chapter, the inventory analysis will propose new myopic inventory models for stochastic pharmaceutical models. Answer to the second question, using a game-theoretic approach for collaborative inventory sharing, is proposed in Chapter 4.

1.3 Chapter Organization

This dissertation is divided into 5 chapters. We introduce the first study, Cost-effectiveness Analysis for Diabetic Foot Ulcer Prevention Strategies and Timely Treatment, in Chapter 2. In this chapter, a detailed literature review of this study, problem statement and cost-effectiveness approach used for this problem are presented. Chapter 3 presents the second

study, Pharmaceutical Supply Chain Problem Under Demand and Supply Uncertainty, and includes a literature review for inventory planning under uncertainty and assortment or catalog problem, two proposed stochastic approaches to find the optimal inventory management strategy, and analysis of results from comparing the proposed strategy with the current inventory policy. Chapter 4, introduces inventory sharing as another approach for facing drug shortages and analysis the interaction among hospitals under different conditions. In Chapter 5, the conclusion of each study and future possible extensions of these studies are explained.

Chapter 2

Long Term Cost-effectiveness Analysis for Diabetic Foot Ulcers: Timely Treatment and Primary Prevention Strategies

Due to the increasing population of diabetic patients, the lower quality of life in patients with foot ulcers, and higher treatment costs for diabetic patients with foot ulcers, receiving adequate and timely treatment and preventive strategies are necessary. In this chapter, background and a literature review of the diabetic foot ulcers and cost-effectiveness analysis are presented. Next, research questions and a model to answer these questions are proposed.

2.1 Background and Literature Review

The growing population of diabetic patients has brought with it an increase in the number of foot ulceration which can result in limb loss and even death. The most costly and feared consequence of a foot ulcer is limb amputation. Diabetic foot ulcers precede 25% to 90% of all amputations (Pecoraro et al., 1990, Unwin, 2000). It can cause marked physical disability and reduction in quality of life (Nabuurs-Franssen et al., 2005, Vileikyte, 2001). Besides the lower quality of life in diabetic patients with foot ulcers, cost of treatment for these patients is more than other diabetic patients because they need more emergency department visits, more frequent admissions to hospital, and longer length of stays. Moreover, treatment is challenging and usually needs to be long lasting. The cost of care in the year after the first ulcer episode for diabetic patients with foot ulcers is 5.4 times higher than patients without foot ulcers and in the second year this factor is 2.8. The treatment cost of the highest grade ulcers is 8 times more than the treatment cost of low-grade ulcers (Driver et al., 2010).

Education along with other preventive strategies such as regular inspection of the feet by health care professionals, optimizing metabolic control, regular podiatric care and adjusted

shoes and insoles are recommended to lower the risk of foot ulceration in diabetic patients (Gershater et al., 2011).

Several review papers have been published on the effect of prevention strategies including education on diabetic foot ulcers (Armstrong et al., 1998, Assal et al., 1985, Bild et al., 1989, Boulton, 1995, Bowering, 2001, Dorresteijn et al., 2010, Edmonds et al., 1996, Larsson and Apelqvist, 1995, Levin, 1995, Mason et al., 1999, Mayfield et al., 1998, O'Meara et al., 2000, Rith-Najarian and Reiber, 2000, Singh et al., 2005, Wu et al., 2007). However, four of these studies were systematic reviews (Dorresteijn et al., 2010, Mason et al., 1999, O'Meara et al., 2000, Singh et al., 2005). The most recent systematic review inferred that little evidence is available to support the effectiveness of patient education for the prevention of diabetic foot ulceration or amputations (Dorresteijn et al., 2010). According to this review paper, different studies in this area are not heterogeneous because of the wide variety of participants, types of control interventions, outcome measures, outcome assessment tools, duration of follow-up and risk of bias between different studies.

While our study is closely related to the studies that have been surveyed in the above mentioned review papers, it differs from these earlier studies in several aspects. First and foremost, the current study includes the most critical sources of variation in other studies as variable factors and proposes a more generalized model. Generalized structure of the model addresses the main shortcoming of other studies that have been noted by Dorresteijn et al. (2010). It enables the decision maker to do sensitivity analysis for different sources of variation and results in a specified prevention strategy. For example Gershater et al. (2011) studied a group of patients with diabetes and high risk of ulceration to investigate if participant-driven patient education in group sessions, compared to provision of standard information, is effective in reduction of new ulceration during 24 months. They concluded that these patients develop foot ulcers in spite of participant-driven group education because high risk patients have external risk factors that are beyond this form of education. The target of this study are high risk diabetic patients (patients with previously healed ulcers) while in our study all diabetic patients are considered whether they are low risk or high risk. However, the model allows the decision maker to asses effectiveness of prevention for

three different groups of patients, based on their unique risk factors.

Second, to the best of our knowledge, none of the existing studies explore the effectiveness of both primary preventive strategies and timely treatment in one study. Primary prevention tries to inhibit the onset of health problems while timely treatment, as a secondary prevention strategy, is trying to restore a person who is already affected to maximum functioning (Aday et al., 2004). In diabetic foot ulcers, primary prevention is reducing the risk that diabetic patients develop foot ulcers while secondary prevention is decreasing the risk of progressing into amputation. Timely treatment for diabetic patients specially those who already have developed foot ulcer is very crucial. Delay in treatment can easily result in amputation and limb loss. The key role of timely treatment as a secondary prevention on diabetic patients has been ignored in previous studies. Providing optimal diabetic limb care require mitigation of risk associated with the development of DFUs, recognition of a DFU when it occurs, timely access to appropriate DFU care and adherence to evidence-based therapy (Wrobel et al., 2011).

Third, using the proposed model we can define a threshold for the cost of prevention strategy and timely treatment for each group of patients. This outcome is advantageous for policy makers. Applying this comprehensive decision support system enables the policy makers to define the optimal set of actions.

2.1.1 Cost-effectiveness Analysis

The ultimate goal of any healthcare system is maximizing the health of a population given a fixed amount of resources. In the operational research literature some papers address techniques for resource allocation in healthcare. Different mathematical programming approaches under deterministic conditions (Epstein et al., 2007, Flessa, 2003, Stinnett and Paltiel, 1996) and stochastic condition (Chalabi et al., 2008, Moreno et al., 2010) have been proposed in literature.

One approach that has been widely used in healthcare to address this issue is Economic Evaluation. Economic Evaluation is identifying, measuring, valuing, and comparing the cost

and consequences of the alternatives being considered (Drummond et al., 2005). Different economic evaluation approaches are used in healthcare such as cost-consequence analysis (CCA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). CCA is simply reporting the costs and consequences of different alternatives and lets the decision maker interpret them in some way. In CMA it is assumed that the outcomes of alternatives are identical and the option which minimizes the costs will be selected. CUA and CEA are sometimes considered the same because in both costs are monetary values and consequences are non monetary. However, CUA is more broad that CEA. CUA adjusts consequences of alternatives by health state preference scores or utility weights while CEA usually evaluates the outcome by one natural unite such as life-years gained or disability-days saved. CUA commonly measures the outcomes by Quality-Adjusted Life Years (QALY) (Drummond et al., 2005).

The concept of QALY was first introduced by Klarman and Rosenthal (1968) although they did not use this term in their research. This measure combines length of life and quality of life in one measure. According to the National Institute for Health and Clinical Excellence (NICE), the QALY is a measure of a person's length of life weighted by a valuation of their health-related quality of life (for Clinical Excellence , NICE). This measure places weight on time in different health states. One year of perfect health is worth 1 and a year of less than perfect health is worth less than 1. Death is equivalent to 0, although some health states are regarded as being worse than death and have negative scores. One of the instruments that NICE suggest to evaluate QALY is EuroQoL (EQ-5D). EQ-5D is a simple, self-administered instrument which provides a composite index score representing a given health state by defining five dimensions of health: mobility, ability to selfcare, ability to undertake usual activities, pain and discomfort, and anxiety and depression.

Among all these methods, cost-effectiveness analysis and cost-benefit analysis have been applied more in studies (Gray et al., 2011). The difference of these two approaches is on how they measure the outcomes. In CEA no monetary value is placed on the health outcomes. It does not let the decision maker know whether health spending is high or low but rather results in how a given budget can maximize the health outcomes. Unlike CEA, CBA

evaluates all costs and benefits in monetary units.

Based on the essence of input and output in this study, we are planning to use cost-effectiveness approach. This approach has been used for diabetic foot ulcer prevention by Ragnarson Tennvall and Apelqvist (2001) and Ortegon et al. (2004). A Markov-based cost-utility simulation model for a 5-year horizon is presented by Ragnarson Tennvall and Apelqvist (2001). They conclude that an intensified prevention, including patient education, foot care and footwear for high-risk patients, is cost-effective if the risk for foot ulcers and lower extremity amputations can be reduced by 25%. Results of another Markov-based model for patients with newly diagnosed type 2 diabetes shows that guideline-based care is cost-effective and even cost saving. Guideline-based care includes intensive glycemic control (IGC), professional protective foot care, education of patients and staff, regular inspection of the feet, identification of the high- risk patient, treatment of nonulcerative lesions, and a multidisciplinary approach to established foot ulcers (Ortegon et al., 2004). As mentioned in section 2.1, these methods are not heterogeneous and they do not consider all risk factors and the result of patient education about each factor. Our study will model a more generalized structure using a cost-effectiveness analysis.

2.2 Problem Statement

As discussed earlier, educating diabetic patients for self-care and timely foot care are considered as fundamental strategies for prevention and reducing the consequences of diabetic foot ulcer. As mentioned in section 2.1, different researchers have studied this problem but there are questions that have not been answered in the literature. The research presented in this chapter deals with proposing a decision support system to address the following questions:

- It is expected that timely and adequate treatment has an effect on reducing the complications resulting from DFU. How much is the effect of timely treatment on each group of patients and what is the optimal treatment strategy to minimize the costs of the system?

- Diabetic patients who did not receive primary education are not aware of the self care procedures and possible consequences of DFU. Moreover, it is expected that preventive strategies have different effects on different types of patients. How much is the optimal investment for giving primary education to each group of diabetic patients?

To answer these two questions, our research is using a cost-effectiveness approach along with sensitivity analysis.

2.3 Proposed Approach

Similar to any other multicriteria approach, the first step of model development is identifying the risk factors that lead to foot ulceration and limb loss. Several risk factors have been mentioned in literature as affecting risk factors. According to Boyko et al. (1999) risk factors affecting foot ulceration are: foot insensitivity, past history of amputation or foot ulcer, insulin use, Charcot deformity, poor arterial circulation, higher body weight, poor vision and orthostatic hypotension. Singh et al. (2005) pointed out risk factors such as ankle brachial index (ABI), using appropriate footwear, plantar pressure, Arterial oxygen supply, biothesiometry, assess lower extremity vascular status and smoking status. Studies show that neuropathy and bony abnormalities of the foot are two very important component causes. In addition to these factors other component causes exist as well (Reiber et al., 1999), (Boyko et al., 2006), (Lavery et al., 2008). It should be noted that none of the risk factors associated with DFUs could be considered as sufficient cause, however, although uncommon, DFUs do occur in patients without significant neuropathy or bony abnormality. In relevant studies from the US and Europe, the overall prevalence of neuropathy varies between 28 and 66% (Azad et al., 1999, Boyko et al., 2006, Ramsey et al., 1999). This rate varies depending on duration of diabetes and age (Young et al., 1993). A large study found that the ABI is a strong risk factor of foot ulceration (Boyko et al., 1999). Reiber et al. (2002) suggests that patients with neuropathy and foot deformities may benefit from custom shoes. Improperly fitting shoes (i.e., a foot size and shoe size mismatch) were found

in 74.5% of U. S. veterans presenting to an interdisciplinary foot clinic. Among diabetics with neuropathic feet, improperly fitting shoes was associated with an odds ratio of 4.8 for the development of foot ulceration (Nixon et al., 2006). A similar incidence of improper fit has also been found in the United Kingdom (Harrison et al., 2007).

Since this model is tailored to support regional diabetic patients, applicable risk factors, determined by our collaborators to categorize the patients are neuropathy and peripheral arterial disease (PAD). Considering these risk factors, diabetic patients can be categorized under three major groups: PACT 1, PACT 2 and PACT 3. PACT 1 are patients with neither neuropathy or peripheral arterial disease. PACT 2 are patients with neuropathy and PACT 3 are patients with peripheral arterial disease (PAD), with or without neuropathy.

In the next step, after defining the risk factors, classifying all patients into three groups the proper incident rate to each group is assigned based on the literature (Table 2.1). If proper data for a big group of patients would be available, distribution fitting can be done on the data to get more detailed information about these incident rates. Next all possible health states for a diabetic patient needs to be identified. All feasible health states that a diabetic patient can experience are illustrated in picture 2.1. As it is shown in the picture, any patient can be in any of these seven states, based on either they receive primary prevention education and timely treatment. Patients who receive foot care, revascularization and wound care, will have the unhealed ulcer or a healed ulcer while there is a chance that they go through limb loss. The incident rate of recurrence of ulcer in these patients is very low so it is assumed equal to zero. Revascularization is a procedure that restores the perfusion to the limbs. It is either in the form of endovascular intervention or surgical bypass and greatly decreases the risk of limb loss. This procedure is required just for PACT 3 patients. The limb loss state can be broken into different components that are out of the scope of this study. Patients who are not receiving any treatment will have either an unhealed ulcer or infected ulcer. It is assumed that infected patents will get antibiotic and go to either stage of the unhealed ulcer, healed ulcer or limb loss during one month. Considering the high probability of recurrence of ulcer for patients who do not receive treatment, patients whose ulcer is healed without getting adequate treatment may get the ulcer again.

Diabetes and foot ulceration is associated with significantly increased mortality (Apelqvist, 1998, Sanders, 1994). From all possible states there is an associated mortality rate for each group of patients. The mortality rate for each group of patients is presented in Table 2.1.

		PACT 1	PACT 2	PACT 3
Ulcer Development Rate		Triangular(0.005,0.008,0.002)	Triangular(0.0015,0.0025,0.006)	Triangular(0.009,0.0123,0.016)
Initial Population		20446	4994	3131
Mortality Rate		Triangular(0.003,0.005,0.008)	Triangular(0.006,0.008,0.01)	Triangular(0.008,0.01,0.012)
With Treatment	Rate of healing	Triangular(0.15,0.15,0.2)	Triangular(0.1,0.15,0.2)	Triangular(0.059,0.109,0.159)
	Rate of limb loss	Triangular(0.007,0.009,0.0011)	Triangular(0.007,0.009,0.0011)	Triangular(0.01,0.012,0.014)
No Treatment	Rate of healing	Triangular(0.1,0.15,0.2)	Triangular(0.05,0.1,0.15)	Triangular(0.024,0.043,0.068)
	Rate of limb loss	Triangular(0.008,0.01,0.015)	Triangular(0.015,0.02,0.025)	Triangular(0.024,0.031,0.068)
	Rate of recurrence of ulcer	Triangular(0.005,0.01,0.015)	Triangular(0.015,0.02,0.025)	Triangular(0.024,0.031,0.068)
	Rate of infection	Triangular(0.068,0.074,0.078)	Triangular(0.1,0.115,0.13)	Triangular(0.125,0.1,0.13)

Table 2.1: Monthly incident rates for three group of patients

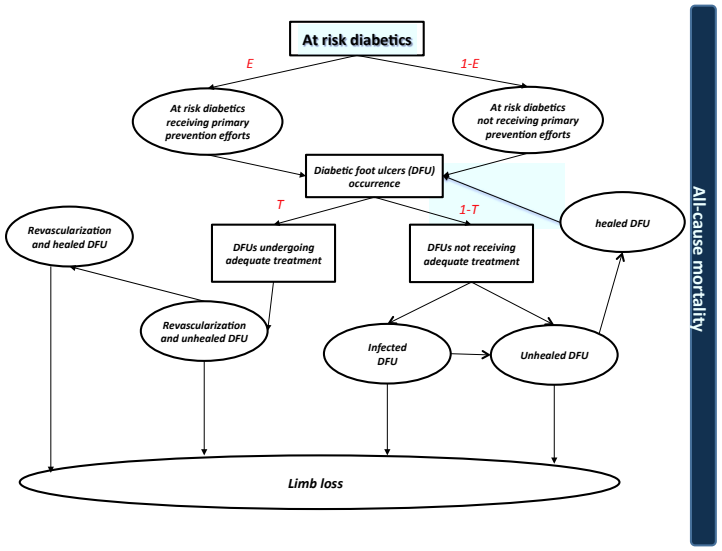

Figure 2.1: Clinical transition states for diabetic foot ulcer patients

After defining the states, the associated cost for patients in each state needs to be defined (Table 2.2). These costs are collected based on multiple studies and expertise of our collaborator.

After defining the inputs of the model, we need to determine a proper measure to evaluate the outcome of the model. Based on the expertise of our collaborators from the Michael E. DeBakey VA Medical Center, the effect of timely treatment in diabetic foot ulcer patients can be measured by total cost, number of amputations and cost per prevented limb

	PACT 1	PACT 2	PACT 3l
Monthly cost of primary prevention	Triangular(4,8,42)	Triangular(4,8,42)	Triangular(4,8,42)
Monthly cost of treatment	Triangular(417,1004,1667)	Triangular(417,1004,1667)	Triangular(721,1421,1971)
Monthly cost of healed ulcer	Triangular(17,42,83)	Triangular(17,42,83)	Triangular(17,42,83)
Cost of infection	Triangular(500,16000,20000)	Triangular(500,16000,20000)	Triangular(500,16000,20000)
Cost of revascularization	NA	NA	Triangular(47,949,44635)
Cost of amputation surgery	Triangular(17,2017,34201)	Triangular(17,2017,34201)	Triangular(17,2017,34201)

Table 2.2: Associated cost for different health states for three group of patients

loss. The significance of prevention strategies results can be measured by total number of ulcers avoided and cost per ulcer avoided. Last step of the approach can be defined as running a sensitivity analysis on the parameters of interest. Two parameters of interest for sensitivity analysis is percentage of patients who receive primary prevention education (E) and probability of receiving timely treatment (T). In section 2.4 the results of the model and sensitivity analysis are presented.

2.4 Numerical Results of Model

Patients are divided into three groups based on identified risk factors by our expert collaborators. A population of initial patients are generated according to distribution of patients in these three groups. The agent-based simulation is run for five years horizon and the unit of time for transition rate is month. Two parameters of interest for sensitivity analysis in this study are percentage of patients receiving timely treatment and percentage of patients receiving primary education. It will help healthcare administrators to choose proper strategy for diabetic foot ulcer patients.

2.4.1 Results for Timely Treatment

Considering different characteristics of the patients in three groups and their different transition rates among states, receiving adequate timely treatment has different effects on the population of each group. The effect of timely treatment is studied on two outcomes of the model: number of limb loss (amputation) and total cost of system.

Number of limb loss in three groups of patients for different treatment rate, is shown

in Fig. 2.2. In this figure, PACT 1 patients will have more amputations when treatment rate increases. This result is expected because of two reasons. The rate of amputation for patients who receive treatment and those who do not receive treatment are slightly different. Also, the rate of healing for patients who received the treatment is very close to patients who did not receive treatment. Based on the transition of patients between states, patients who have not received treatment but their wound has been healed, will not go through amputation except they develop an ulcer again. Therefore, patients who receive treatment will be cumulated in two states, healed and unhealed, while there is a loop of states for patients who do not receive treatment. Consequently, number of patients who are in two states of receiving treatment will be more than number of patients in two states of having unhealed ulcer and having infection. It causes the increase in number of limb loss when rate of timely treatment increases for this group of patients. Number of amputations in PACT 2 patients will decrease when treatment rate increases, although this decrease is not as much as PACT 3 patients. Higher incident rate of amputation for non treated patients in PACT 3 group can justify this decrease in number of patients. Therefore, offering timely treatment to higher number of PACT 3 patients has the maximum impact in decreasing total number of amputation in all three groups.

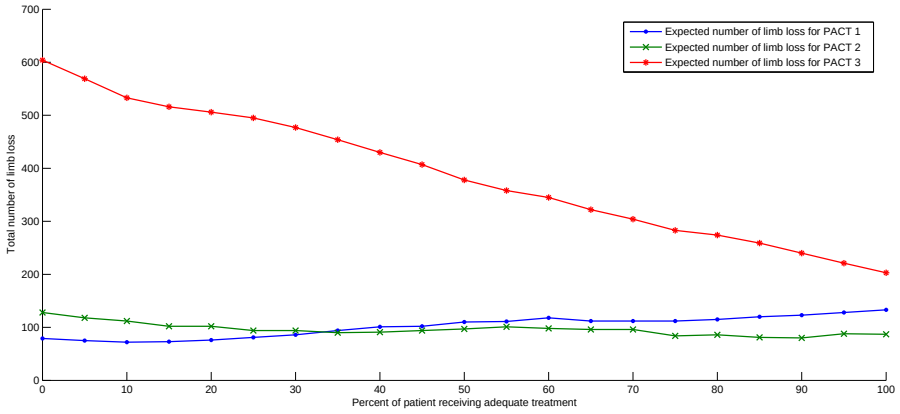

Figure 2.2: Sensitivity analysis of limb loss relative to percent of patients receiving timely treatment

The next measure that helps in strategic planning of timely treatment in a hospital is the

total cost of the system under different treatment rates. For PACT 1 patients, considering the positive correlation of number of amputation and treatment rate in this group, the total cost of the system increases when more treatment is given to this group of patients. The minimum cost for this group of patients happens when treatment rate is around 10%. What makes this rate 10% instead of 0% is the infection cost. for this group, two main costs that determine the optimal treatment rate are infection cost and amputation cost. When rate of treatment increases the number of amputations increases, while infected patients decreases. The break even point of these two costs happens around 10% rate of treatment. The changes in total cost for PACT 1 patients is illustrated in Fig. 2.3.

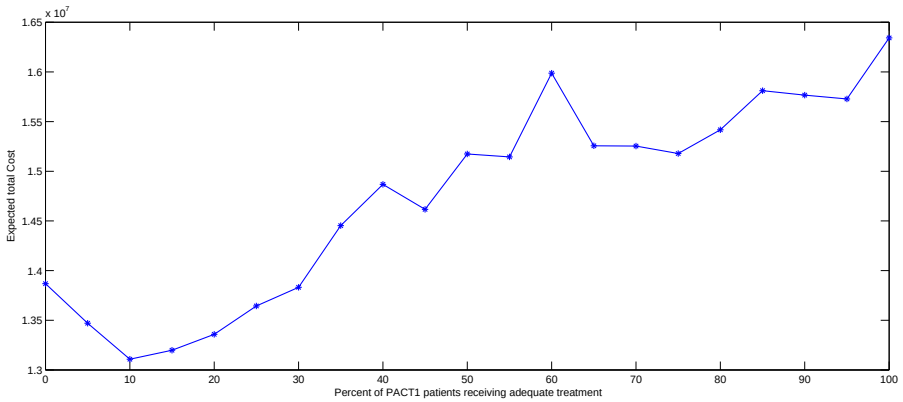

Figure 2.3: Sensitivity analysis of cost relative to percent of PACT 1 patients receiving timely treatment

The same analysis should been done for PACT 2 patients. As shown in Fig. 2.2, the number of amputation in this group increases. Therefore, an increase in the rate of treatment for this group of patients will result in lower amputation cost. On the other hand, a higher treatment rate will result in a lower infection cost. Accordingly, the total cost will decrease when the treatment rate increases for this group of patients. The pattern of this decrease is shown in Fig. 2.4.

In the cost analysis of PACT 3 patients, revascularization surgery cost is a component that does not happen for PACT 1 and PACT 2 patients. As discussed earlier, the main procedure in treatment of PACT 3 patients is revascularization. The foremost stage of treatment for all PACT 3 patients is revascularization which is a very expensive procedure.

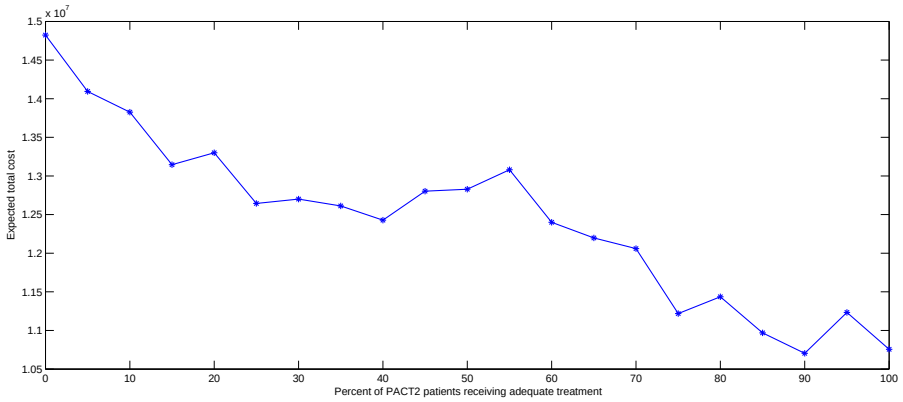

Figure 2.4: Sensitivity analysis of cost relative to percent of PACT 2 patients receiving timely treatment

Considering the negative correlation of amputation with timely treatment rate in PACT 3 patients, the cost of amputation for this group of patients decreases while treatment rate increases. However, the cost of revascularization will increase while rate of treatment increases. Hence, the minimum cost of the system will happen at break even point of amputation cost and revascularization cost which is around 64 million dollar during five years when treatment rate is 10%. The trend of total cost for different treatment rates is illustrated in Fig. 2.5.

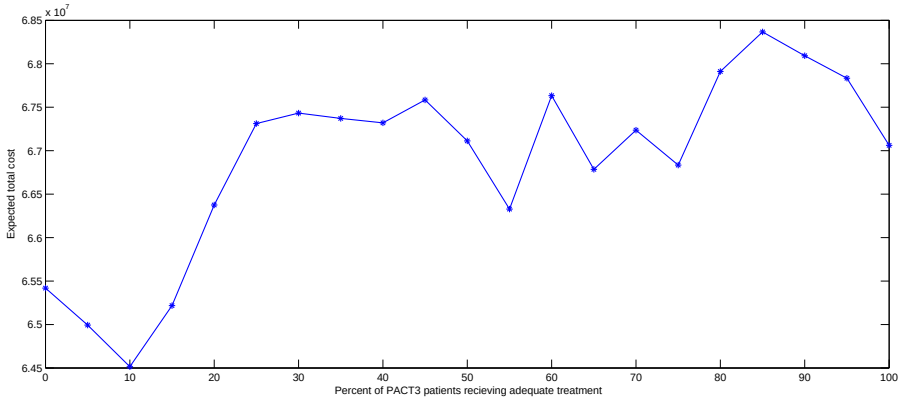

Figure 2.5: Sensitivity analysis of cost relative to percent of PACT 3 patients receiving timely treatment

Another measure of interest for heathcare decision makers is the cost of each prevented

limb loss. For PACT 1 patients, it is easy to see that both minimum number of amputations and minimum cost happen when treatment rate is 10%. Therefore considering this measure also, treatment rate of 10% is the optimum rate of treatment for PACT 1 patients. Fig. 2.6 illustrates the index of cost over prevented amputations for PACT 2 and PACT 3 patients. When the value is negative, it means that cost of system is less that when no treatment is given and also number of amputations is less. Therefore in that rate of treatment, prevented amputations do not only have cost, but also it decreases the cost of the system. As it is shown in Fig. 2.6 the maximum benefit for PACT 2 patients happens when all patients get treatment. For PACT 3 patients, the benefit per prevented amputation happens only when the rate of receiving treatment is $5\%, 10\%$ or 15%. The maximum benefit happens when the rate of receiving treatment is 10%. This results are similar to the conclusions derived from analyzing the amputation number and total cost for each group.

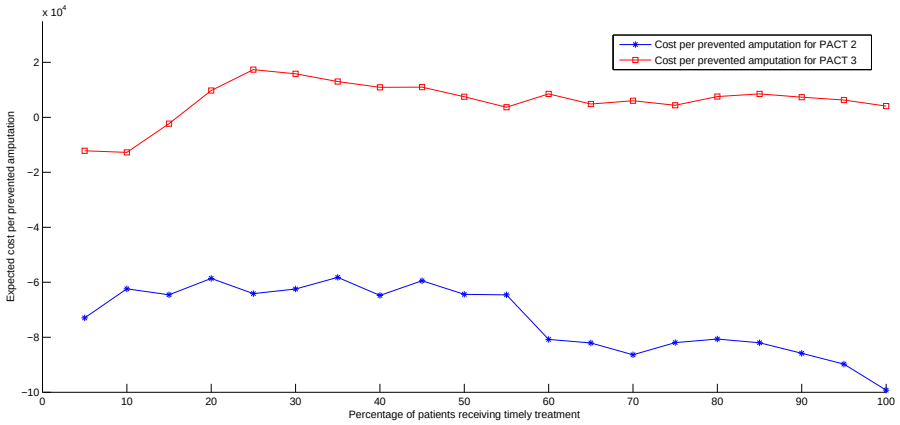

Figure 2.6: Sensitivity analysis of number of prevented amputation relative to percent of patients receiving timely treatment

2.4.2 Results for Primary Prevention

The second parameter of interest in the analysis is the percentage of patients assigned for a primary prevention program like education for self care. In this model, the effectiveness of primary prevention is assumed 20%. This means that primary prevention will decrease the rate of ulcer development by 20%. The goal is finding the optimal percentage of patients

that should receive primary prevention. To find the optimal percentage of the patients receiving primary prevention, the timely treatment rate of each group is set to the optimal value found in section 2.4.1. Fig. 2.7 illustrates the changes in total cost of the system for the percentage of patients receiving primary prevention changes. For PACT 1 and PACT 2 patients the total cost increases while for PACT 3 patients this value decreases. Therefore, if the only measure for picking the optimal strategy is total cost, all PACT 3 patients should receive primary prevention while PACT 1 and PACT 2 patients should not receive any primary prevention. Since the measure for healthcare decision makers is maximizing the quality of service, the number of ulcers prevented under each strategy also should be analyzed.

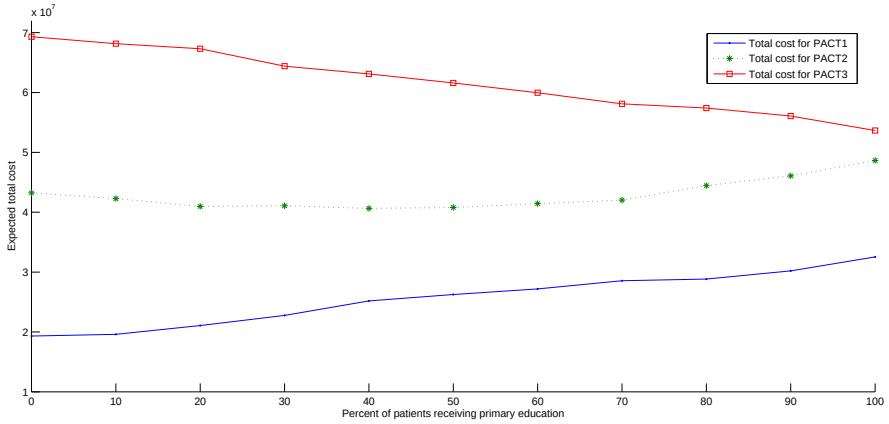

Figure 2.7: Sensitivity analysis of cost relative to percent of patients receiving primary prevention

The expected number of prevented ulcers under each strategy is shown in Fig. 2.8. The number of patients who have been saved from developing an ulcer is increasing when the percentage of patients receiving primary prevention is increasing. To find the optimal strategy the cost per prevented ulcer is calculated and shown in Fig. 2.9. According to this graph, if around 90% of patients in each group receive primary prevention, the cost per ulcer prevented will be minimized. Another conclusion derived using this graph is priority of the patients in receiving primary education. The lowest cost per prevented ulcer is for PACT 1 patients. Therefore, this group have priority over other groups in receiving

primary prevention. For education rate more than 15% PACT 2 patients has maximum cost per prevented ulcer. Therefore, this group is not preferred to receive primary prevention untill other groups receive primary prevention. For education rates more than 70% cost per prevented ulcer for PACT 1 and PACT 3 are converging so there is no difference in these patients in higher rates of providing primary prevention. Another use of this graph is helping healthcare decision makers to find the threshold for offering preventive strategies. Based on the value of each ulcer prevented at the healthcare facility, the optimal percentage of patients who should receive primary prevention can be found.

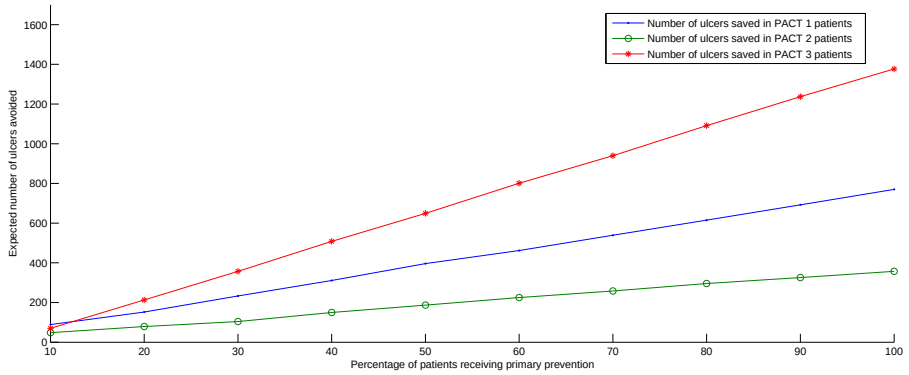

Figure 2.8: Sensitivity analysis of number of avoided ulcers relative to percent of patients receiving primary prevention

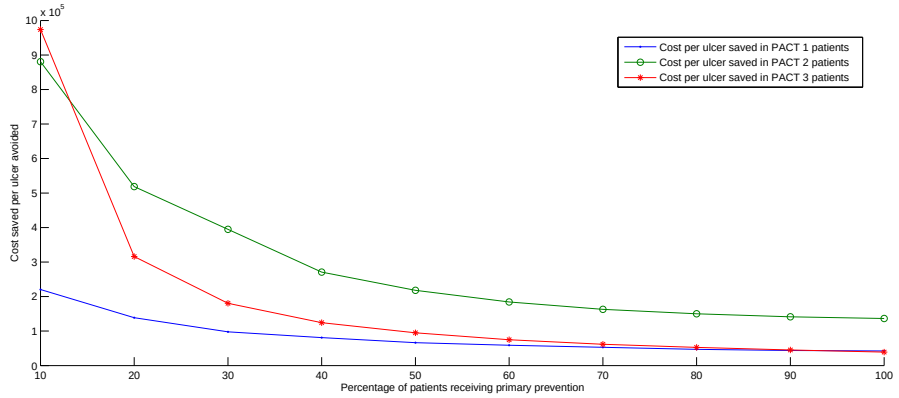

Figure 2.9: Sensitivity analysis of cost per prevented ulcer relative to percent of patients receiving primary prevention

2.5 Concluding Remarks

In this chapter the effect of two effective parameters on diabetic foot ulcers, receiving timely treatment and primary prevention, is studied. The contribution of the present research is studying two key parameters in diabetic foot ulcer development in a single framework. Accordingly, the model has flexibility to predict the outcome of different combination of strategies associated with providing timely treatment and primary prevention for diabetic patients. According to the results, around 10% of PACT 1 who are low risk patients should receive timely treatment to minimize the expected total cost of the system. For this group of patients, 10% is the break even point for expected amputation cost resulted from getting treatment and expected infection cost resulted from not getting treatment. This point is also giving the maximum benefit per prevented amputation. All PACT 2 patients need to receive timely treatment to minimize the expected total cost of the system, expected number of amputations and maximize benefit of prevented amputations. Ten percent of PACT 3 patients should receive timely treatment. This point is the break even point for expected revascularization cost for treated patients and expected amputation cost for non treated patients and also the maximum benefit per prevented amputation happens in this point.

The recommended strategy for using primary prevention, is applying preventive strategies for around 90% of patients in all groups. Applying these strategies will result in more cost while it will decrease number of developed ulcers. The minimum value of cost for ulcer prevented for all groups happens when around 90% of patients receive primary prevention. Besides, PACT 1 patients having priority over PACT 2 and PACT 3 patients in receiving primary prevention since the cost per prevented ulcer in this group is less than other groups. Also healthcare administrators can define a value for each prevented ulcer and find their optimal prevention strategy according to Fig. 2.9. Generally, optimal strategy for providing timely treatment and prevention strategies depends on the risk parameters of the patient and the group which patient belongs to.

Chapter 3

Pharmaceutical Inventory Problem under Supply and Demand Uncertainty

This chapter addresses a pharmaceutical inventory management problem under supply and demand uncertainty. First the background of the pharmaceutical supply chain and relative literature about the pharmaceutical inventory problem under supply and demand uncertainty are introduced. Then one reorder point model using a continuous time Markov chain is proposed and its results are compared with current inventory strategy as well as an (s, S) policy from the literature (Arreola-Risa and DeCroix, 1998). Next, a more general model using a continuous time Markov chain is proposed and is solved using a heuristic approach. The numerical results of this model is compared with current strategy and finally the sensitivity analysis of different parameters of the model in presented.

3.1 Background and Literature Review

The study of pharmaceutical supply chain has typically been approached from either managerial analysis perspective (Jaber, 2009). Some managerial approaches include outsourcing (Li and Benton, 1996, Lunn, 2000, Nicholson et al., 2004), vendor managed inventory (VMI) (Kim, 2005), supply chain integration (Meijboom and Obel, 2007) and risk in pharmaceutical supply chain (Breen, 2008). Inventory investments in healthcare industry are estimated to be between 10% and 18% of net revenues (Holmgren and Wentz, 1982, Nicholson et al., 2004). This percentage is even higher for hospitals. Nathan and Trinkaus (1996) estimated the inventory management costs for anywhere between 17% and 35% of a hospital's total revenue.

A number of quantitative models have been introduced to find the optimal inventory planning in a hospital. However, there do exist a few models in the inventory planning literature that are relevant to the proposed work. First, Dellaert and van de Poel (1996) introduced an economic order quantity model for inventory control of an academic hospital in Netherlands. Elsewhere, practical ideas have been introduced by Jayaraman et al. (2000) to improve the flow of materials in a healthcare facility. Lapierre and Ruiz (2007) develop a model that optimizes the inventory control and logistics scheduling in a multi echelon inventory problem to minimize inventory costs and balance the workload over the weekdays. However, importantly, none of the models that are specified for pharmaceutical supply chain take into account the uncertainties in the supply chain.

Uncertainty can be short-term or long-term based on the time-frame over which the uncertainty affects the system (Subrahmanyam et al., 1994). Long-term uncertainties such as uncertainty in demand and changes in availability of a pharmaceutical item can be considered in inventory control models to find the optimal ordering policy to minimize the shortages caused by these uncertainties. There also exist short-term uncertainties such as recession but this is out of our scope of work. We consider drug shortages due to long-term uncertainties including but not limited to material availability, production decisions, and FDA approval strategies. Long-term uncertainties in a hospital can be grouped in two main groups in the supply chain context: uncertainty in demand and uncertainty (as disruptions) in supply.

Demand uncertainty is one of the major challenges in pharmaceutical inventory planning. Demand uncertainty is studied in general forecasting studies (Syntetos et al., 2009, 2010, Willemain et al., 2004, Zhao and Lee, 1993), in system dynamics (SD) (Catt, 2007, Gardner Jr, 1990, Johnston, 1980), and in inventory control theory (Sani and Kingsman, 1997). The widely-accepted distribution for demand in the literature is Poisson due to its appropriateness of assumptions (i.e., demands of 0 or

1), except a few studies where settings are different and compound Poisson distribution (e.g., negative binomial distribution) is appropriate (Sani and Kingsman, 1997, Syntetos et al., 2009).

Supply uncertainty is presented in two forms in the literature: yield uncertainty and disruption. Yield uncertainty is considered when the quantity of supply delivered is a random variable and can deviate from the order. Disruption is considered when the supply is subject to partial or complete failure. Disruptions are typically modeled as events which occur randomly and may have random length. Table 3.1 shows some of the studies that have introduced a model to solve inventory control problem with disruption in supply.

Article	**Supplier**	**Period**	**Demand**	**Policy**
(Parlar and Berkin, 1991)	single	multiple	deterministic	EOQ
(Weiss and Rosenthal, 1992)	single	finite-horizon	deterministic	EOQ
(Parlar and Perry, 1995)	single	multiple	deterministic	(Q, r, T)
(Berk and Arreola-Risa, 1994)	single	multiple	deterministic	EOQ
(Parlar et al., 1995)	single	finite-horizon	random	(s, S)
(Parlar and Perry, 1996)	2	finite-horizon	deterministic	(Q, r)
(Gupta, 1996)	single	mutiple	random	(Q, r)
(Parlar, 1997)	single	single	random	(Q, r)
(Gurler and Parlar, 1997)	2	multiple	deterministic	(Q, r)
(DeCroix and Arreola-Risa, 1998)	single	multiple	random	(s, S)
(Arreola-Risa and DeCroix, 1998)	single	infinite-horizon	random	(s, S)
(Gullu et al., 1999)	single	multiple	dynamic	(Q, r)
(Mohebbi, 2004)	single	multiple	random	(Q, r)
(Tomlin, 2006)	2	infinite-horizon	random	EOQ
(Ross et al., 2008)	single	finite-horizon	random	EOQ
(Qi et al., 2009)	single	multiple	deterministic	EOQ
(Schmitt et al., 2010)	single	single	random	EOQ
(Schmitt and Snyder, 2010)	3	infinite-horizon	deterministic	(Q, r)
(Yeo and Yuan, 2010)	single	multiple	random	(Q, r)

Table 3.1: Inventory management under disruption literature

Studies in Table 3.1 consider disruptions of different forms (e.g., simple disruptions from the supplier, natural disasters destroying the inventory etc.), different assumptions on lead time, and demand cancellation. We do not elucidate the contribution of each paper separately, but only present key differences in Table 3.1. Furthermore, there are studies that use integrated modeling for inventory and transportation decisions (e.g., (Geunes and Zeng, 2001, 2003)) investigating the effect of backlogging and expediting policies on inventory and transportation costs.

Another key concept that should be considered in pharmaceutical inventory planning is substitutability of drugs. The early roots of the literature on lot-sizing with product substitution can be seen in Assortment or Catalog problems. Assortment or catalog problem is defined as determining which of the possible set of sizes or qualities of some product should be stocked when it is not possible or desirable to stock all of them and substitution in one direction (larger for smaller or higher-quality for lower-quality) is possible at some cost (Pentico, 2008). This problem is first introduced by Sadowski (1959) though this concept is presented by Hanssmann (1957). Because of the nature of substitution in pharmaceutical supply chain, our model is different from available literature handling substitution in different aspects. To address these differences we can study the literature based on three major parameters that can be used in classifying assortment problems.

First aspect is the type of substitution, consumer-driven or firm-driven. Majority of the researches have been done in consumer-driven substitution in which customers might accept or reject the substitutes (Dong et al., 2009, Hopp and Xu, 2008, Huang et al., 2011, Khouja et al., 1996, Kok and Fisher, 2007, Mahajan and Van Ryzin, 2001, McGillivray and Silver, 1978, Nagarajan and Rajagopalan, 2008, Parlar, 1988, Parlar and Goyal, 1984, Smith and Agrawal, 2000). Despite the prevalence of consumer-driven substitution, it is not useful in pharmaceutical inventory management because the probability of impropriety of substitute for a customer is too low and customer is not a decision maker in substitution of a drug.

Firm-driven substitution, called one-way or downward substitution, assumes that all items can be sorted in different classes and lower class items with surplus inventory will be substituted for upper class items (Bassok et al., 1999, Bitran and Dasu, 1992, Dutta and Chakraborty, 2010, Hsu and Bassok, 1999, Hsu et al., 2005, Lang and Domschke, 2010, Pentico, 1974, Rao et al., 2004).

Second parameter that divides the literature to two streams is stochasticity. Several studies propose stochastic models dealing with demand and supply uncertainties while others are deterministic models. Pentico (1974) formulated the problem as a deterministic inventory optimization model in a continuous time setting and uses dynamic programming (DP) approach to solve it. In (Chand et al., 1994) an EOQ-based optimization model is proposed to find the optimal purchase quantities of the parts during an infinite time horizon and stationary cost and demand parameters. Hsu et al. (2005) and also Lang and Domschke (2010) formulate a deterministic, single-level, multiproduct, multi-period dynamic lot-sizing problem. In pharmaceutical inventory planning we face uncertainty both in demand and supply and deterministic models are not able to handle the problem.

Third factor is the time horizon. (Hsu and Bassok, 1999) and also (Bassok et al., 1999) develop a single period multiproduct inventory model with considering downward substitution and stochastic demand. A two-stage integer stochastic program for a single period multi-product inventory problem with stochastic demand and setup cost for production is proposed at (Rao et al., 2004). In this model the first stage variables determine which products to produce and how much to produce, and the second stage variables determine how the products are allocated to satisfy the realized demand. Another single period, two-item model in a fuzzy environment is proposed at (Dutta and Chakraborty, 2010). Because of the critical role of the items that face uncertainty in supply, single-period inventory models can not give a longtime inventory plan to hospitals.

Quantitative models on inventory management in hospitals is limited. It is also noteworthy that aforementioned models have limitations for managing a pharmaceutical supply chain. First and foremost, the goal of a healthcare facility is not the minimization of total costs (e.g., inventory holding, ordering). This does not imply all items have zero cost nor an inefficient and costly policy is acceptable, however, the

primary concern is the quality of service. The second aspect that differentiates the pharmaceutical supply chain is the cruciality of demand satisfaction. Shortages in pharmaceutical supply chain affect patients' lives directly, thus must be avoided. In other supply chains, shortages do not have that significant restriction in the model. For instance, shortages typically cause loss of customer in an apparel supply chain, which has an associated cost. Depending on the tradeoff between revenues, holding, ordering, and shortage costs, a lower inventory level leading to loss of some customers might be a feasible option. On contrary, the main goal of a pharmaceutical supply chain is to minimize shortages. Another aspect that sets pharmaceutical chains apart is that some of the items in shortage can be substituted with alternatives. To the best of our knowledge, a model that considers shortages in an uncertain chain with substitutable items has not been introduced in the literature. Despite the existence of some studies in the literature that consider uncertainties in supply chain, our work is unique with demand disruption and substitution.

3.2 Problem Statement

A paramedical supply chain roughly consists of four main levels: chemical plants, pharmaceutical plants, marketing affiliates and healthcare users. As we explore in this dissertation, the pharmaceutical shortage can be addressed through varying strategies introduced in each of these levels. The hospital is the level that is in direct contact with patients and where the effect of shortage is the highest. Despite the important role of the hospital in solving the pharmaceutical shortages, formulating strategies from the hospital's perspective has been given little attention by researchers. This is likely a result of the complexity of the problem, which involves hospital size, geographic location, diversification, and various specializations (DeScioli, 2005). Therefore, in the first phase of our research, we propose to offer new stochastic models for inventory management of pharmaceutical goods at a single hospital.

In any healthcare organization, two main objectives are the base of all performance measures: lower cost and improving the quality of service. Because of the critical role of healthcare organizations before the 1980s the only objective was maximizing the quality of service. However, the doubling of healthcare costs in the 1970s, and again in the 1980s, led to the need to more formally account for healthcare expenses (Li and Benton, 1996). To develop a model to optimize the pharmaceutical ordering strategies of a hospital, these two main objectives should be considered: *minimizing the holding costs and shortage costs*. Current inventory control policy relevant to the pharmaceutical supply chain makes use of an (s, S) policy, which requires that when the inventory level is s or below, an order should be placed to bring the inventory level up to S. Arreola-Risa and DeCroix (1998) have introduced a model to solve an (s, S) policy with optimality conditions to solve an inventory control problem with supply disruption, backorder and lost sales. The two models proposed in this part of the research investigate the important multi-item generalization of this work, which are applicable for healthcare providers that are required to maintain a number of critical drugs. First proposed model utilizes drug substitution but disregards holding and substitution costs. It considers up to 2 drugs (one mainstream and one substitute/alternative) for each patient/case. The model we propose considers random shortages for substitutes as well as the mainstream drugs using a continuous time Markov chain. Note that the objective function that should be minimized is the total shortage cost. Second proposed model is a more general form of the first model with less assumptions. The objective function of this model minimizes the total cost of the system. Moreover this model considers the order quantity as one of the decision variables and tries to find the optimal order quantity and safety stock level for each drug. Though these two models are different, they are sharing following common assumptions:

- There is uncertainty in demand for each pharmaceutical item. We assume

demands are independent among items. Arrival of demand for each item i is Poisson distributed with rate α_i.

- Shortages for pharmaceuticals are occurring randomly with uncertain durations. We assume the supply disruptions and their durations for drug i are independent and exponentially distributed with rate λ_i and μ_i, respectively.
- Each mainstream item has one substitute that can be used instead of the main drug at a cost of π_i. Substitute items can also be unavailable independent from the main item. Supply disruptions and their durations for substitute drugs are independent and exponentially distributed with rate λ_i' and μ_i', respectively.
- For each item there is an associated shortage impact. The impact of a shortage on mainstream drugs is the same as that of its substitute. The pharmaceutical items under consideration are crucial such as chemotherapeutic drugs. Impacts are difficult to quantify but an subjective assessment is possible based on how QALY of a patient is affected without the drug, and how difficult it is to find the drug from other sources (if any) in an emergency.
- In practice, pharmaceutical items come in lots but lot sizes are not strict. Therefore, we assume items can be ordered in any quantity.
- Lead time is negligible when drugs are available since deliveries are made every other day and overnight deliveries are possible as long as the item is not in shortage.
- When a shortage is over, an order is placed immediately to reach the order-up-to level.
- A limited storage capacity of V is under consideration.
- A continuous inventory review policy (i.e., (Q, R) policy) is employed for practical reasons, although, in practice, the inventory is reviewed periodically.

- There is no differentiation between mainstream and substitute drugs for mathematical convenience. When both are on hand, the total number of items is used rather than exact number of mainstream and substitute items.
- Perishability of drugs has not been considered. Drugs' shelf lives are assumed long enough that the inventory is usually depleted before drugs expire.
- There is a single supplier.

3.3 First Solution Approach

In this section, we present a novel stochastic approach using a continuous time Markov chain to manage the inventory of a healthcare facility that utilizes drug substitution but disregards holding and substitution costs. The proposed model utilizes the following approximations for the sake of mathematical simplicity and computational tractability.

- As the goal is to minimize shortages, amount of inventory on hand is ignored when the drug (mainstream or substitute) is available.
- Order quantity (Q) has virtually no direct effect on the number of shortages. Therefore, it is assumed to be an input parameter typically set to 1 day of supplies. Our aim is to keep inventory holding costs at a reasonable level and avoid excessive holding costs for available items. This can be carefully adjusted with minimal effect on the shortages (e.g., model can be solved using the demand of 2 days and orders can be placed once in 4 days alternately for two sets of drugs since this also ensures feasibility).
- When there is a shortage of both mainstream and substitute item, the inventory level is assumed to drop to reorder point (R) instantaneously.

The main goal is to cope with national drug shortages. The idea is holding more safety stock for crucial items and finding the perfect balance between items so that

the drawbacks of shortages are minimized. The decision for holding an item is affected by the shortage likeliness, probable duration of a shortage, demand rate, substitute availability, and volume of the drug as discussed in the sequel.

3.3.1 Proposed Model

To the best of our knowledge, two underlying facts with regard to a pharmaceutical supply chain are not considered in the literature. First, some of the substitutes may also face random supply. Second, minimization of shortages is the primary goal. In order to satisfy these two shortcomings of the previously proposed models, we propose a reorder point model that considers up to 2 drugs (one mainstream and one substitute/alternative) for each patient/case. The model we propose considers random shortages for substitutes as well as the mainstream drugs using a continuous time Markov chain. Note that the objective function that should be minimized is the total shortage cost. Fig. 3.1 illustrates the transition-rate diagram for the reorder point model.

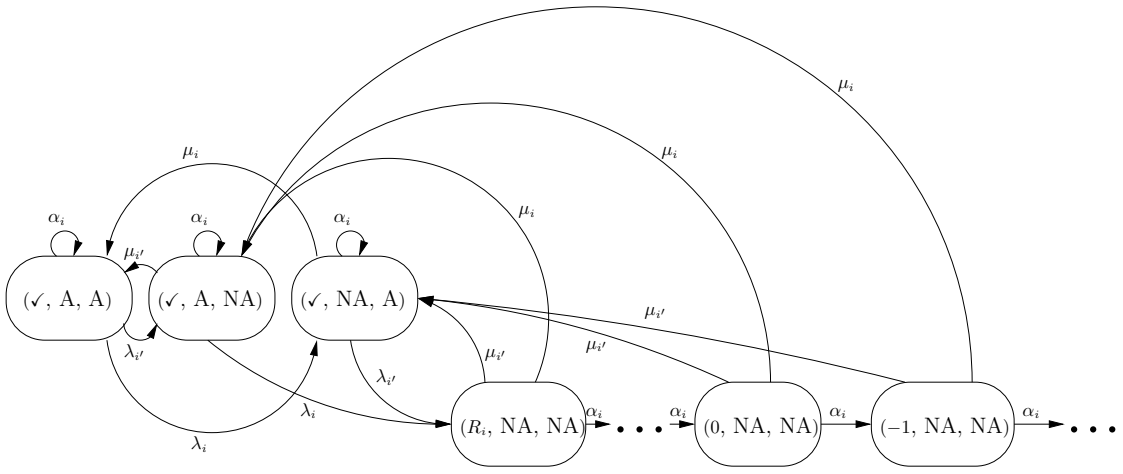

Figure 3.1: Transition-rate diagram for item i in the inventory system for reorder point model.

In this model, states are denoted as triplets where the first entry denotes the inventory level, the second and third entry denote the availability of the mainstream

and substitute item, respectively. It should be noted that when the item or the substitute is available for ordering, the inventory level is between R_i and $Q_i + R_i$. We denote the case where the inventory level is between R_i and $Q_i + R_i$ with ✓, since the exact inventory level and the associated cost is out of our scope. α_i is the daily demand rate for the drug under consideration, which may be drug i (mainstream) and i' (substitute) depending on availability. λ_i and $\lambda_{i'}$ denote the shortage rate for mainstream drug i and it's substitute i', respectively. Similarly, μ_i and $\mu_{i'}$ denote the shortage recovery rate of mainstream and substitute drugs.

In order to find the expected number of items in shortage per day, we first find the stationary probabilities using the transition-rate diagram in Fig. 3.1.

$$(\lambda_i + \lambda_{i'})\mathrm{P}_{(R_i,\mathrm{A,A})} = \mu_{i'}\mathrm{P}_{(R_i,\mathrm{A,NA})} + \mu_i\mathrm{P}_{(R_i,\mathrm{NA,A})} \tag{3.1}$$

$$(\mu_{i'} + \lambda_i)\mathrm{P}_{(R_i,\mathrm{A,NA})} = \mu_i\Omega_i + \lambda_{i'}\mathrm{P}_{(R_i,\mathrm{A,A})} \tag{3.2}$$

$$(\lambda_{i'} + \mu_i)\mathrm{P}_{(R_i,\mathrm{NA,A})} = \mu_{i'}\Omega_i + \lambda_i\mathrm{P}_{(R_i,\mathrm{A,A})}, \tag{3.3}$$

where $\Omega_i = \sum_{j=0}^{\infty} \mathrm{P}_{(R_i-j,\mathrm{NA,NA})}$. From (3.1), (3.2), and (3.3), we have

$$\mathrm{P}_{(R_i,\mathrm{A,A})} = \frac{\mu_i\mu_{i'}}{\lambda_i\lambda_{i'}}\Omega_i \tag{3.4}$$

$$\mathrm{P}_{(R_i,\mathrm{A,NA})} = \frac{\mu_i\lambda_i + \mu_i\mu_{i'}}{(\mu_{i'} + \lambda_i)\lambda_i}\Omega_i \tag{3.5}$$

$$\mathrm{P}_{(R_i,\mathrm{NA,A})} = \frac{\mu_{i'}\lambda_{i'} + \mu_i\mu_{i'}}{(\mu_{i'} + \lambda_i)\lambda_{i'}}\Omega_i. \tag{3.6}$$

Using $\mathrm{P}_{(R_i,\mathrm{A,A})} + \mathrm{P}_{(R_i,\mathrm{A,NA})} + \mathrm{P}_{(R_i,\mathrm{NA,A})} + \Omega_i = 1$, (3.4), (3.5), and (3.6) we obtain the following:

$$\Omega_i = \frac{\lambda_i\lambda_{i'}(\lambda_i + \mu_{i'})}{\lambda_i\lambda_{i'}(\mu_i + 2\mu_{i'} + \lambda_i) + 2\lambda_i\mu_i\mu_{i'} + \lambda_{i'}\mu_i\mu_{i'} + \mu_i{\mu_{i'}}^2} \tag{3.7}$$

Using the definition of Ω_i

$$\mathrm{P}_{(R_i-j,\mathrm{NA},\mathrm{NA})} = \left(\frac{\alpha_i}{\mu_i+\mu_{i'}+\alpha_i}\right)^j \left(\frac{\mu_i+\mu_{i'}}{\mu_i+\mu_{i'}+\alpha_i}\right)\Omega_i \qquad j=0,...,\infty. \tag{3.8}$$

Given R_i, the expected number of items in shortage per day can be calculated as follows:

$$N_i(R_i) = \sum_{j=1}^{\infty} j\mathrm{P}_{(-j,\mathrm{NA},\mathrm{NA})} = \left(\frac{\alpha_i}{\mu_i+\mu_{i'}+\alpha_i}\right)^{R_i} \left(\frac{\mu_i+\mu_{i'}}{\mu_i+\mu_{i'}+\alpha_i}\right)\Omega_i \sum_{j=1}^{\infty} j\left(\frac{\alpha_i}{\mu_i+\mu_{i'}+\alpha_i}\right)^j \tag{3.9}$$

$$= \left(\frac{\alpha_i}{\mu_i+\mu_{i'}+\alpha_i}\right)^{R_i} \left(\frac{\mu_i+\mu_{i'}}{\mu_i+\mu_{i'}+\alpha_i}\right)\Omega_i \frac{\alpha_i(\mu_i+\mu_{i'}+\alpha_i)}{(\mu_i+\mu_{i'})^2} \tag{3.10}$$

$$= \frac{\alpha_i\Omega_i}{\mu_i+\mu_{i'}}\left(\frac{\alpha_i}{\mu_i+\mu_{i'}+\alpha_i}\right)^{R_i} \tag{3.11}$$

The optimal reorder points that minimize the expected impact of shortages can be obtained solving

$$\min_{\mathbf{R}} \quad \sum_{i=1}^{m} \pi_i N_i(R_i) \tag{3.12a}$$

$$\text{subject to} \quad \sum_{i=1}^{m} v_i\left[Q_i+R_i\right] \le V \tag{3.12b}$$

$$R_i \ge 0 \qquad i=1,...,m, \tag{3.12c}$$

where $N_i(R_i)$ is the expected number of items in shortage per day as defined in (3.11) and Ω_i is defined in (3.7). Q_i is set to the daily demand α_i as discussed above. π_i is the cost of shortage for item i that is obtained by quantifying the impacts in Table 3.2 and m is the number of mainstream drugs. It should also be noted that substitute items (i'), which are not used unless there is shortage on mainstream drugs (i), are considered implicitly in the model. Next, we customize the most suitable model from the literature for the scenario on hand. We will compare both solutions with the current policy to highlight the benefits in section 3.3.3.

3.3.2 An Optimal (s, S) policy

Arreola-Risa and DeCroix (1998) propose an (s, S) policy for items with supply disruption and demand uncertainty. The employed inventory policy (with a continuous review approximation similar to our model) and the assumptions on demand and supply make the model very suitable for the healthcare pharmaceuticals. On the other hand, the following aspects of the model are the shortcomings within the healthcare supply chain context:

- Substitute items are not considered.
- There is unlimited capacity for storage.
- The model considers a single item.
- The objective is to find the optimal stock levels for an item to perfectly balance the tradeoff between ordering cost, inventory holding cost, and lost sales cost.

Fig. 3.2 illustrates the transition-rate diagram for the model presented in (Arreola-Risa and DeCroix, 1998).

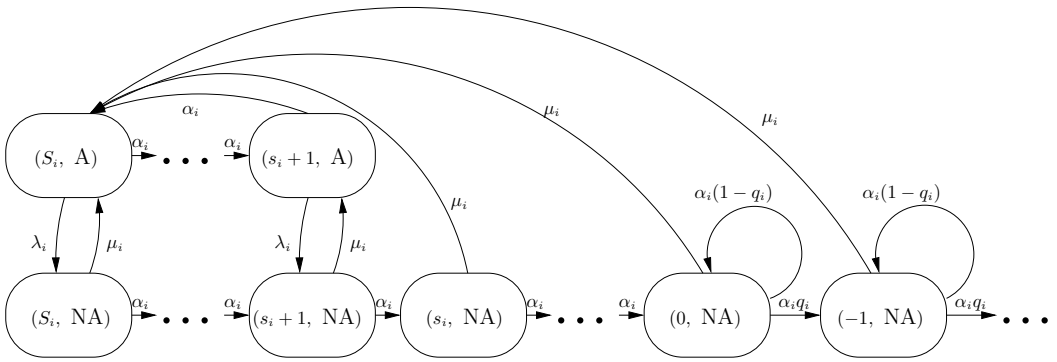

Figure 3.2: Transition-rate diagram for item i in the inventory system for (s, S) model.

The states are denoted using the exact number of items on hand and the availability of the item. This model is a perfect representation of a retailer's continuous review

policy with uncertain demand (with rate α_i), random disruptions in supply (occurring with rate λ_i and expected duration of $1/\mu_i$), and lost customers (with probability $1-q_i$).

The model proposed in this section investigates the important multi-item generalization of this work with substitute information, which is applicable for healthcare providers that are required to maintain a number of critical drugs. Substitute shortages cannot be incorporated directly into the model but assuming substitutes are not stocked, we let the probability of availability of a substitute is $1-q_i$. In an effort to utilize shortage information for substitutes, $\mu_{i'}$ and $\lambda_{i'}$ we set q_i to the long term fraction of time the substitute is unavailable, thus $q_i = \lambda_{i'}/(\mu_{i'}+\lambda_{i'})$[1].

In order to handle multiple items, we constrain the total capacity used. The cost of ordering is available and unit holding cost per unit time is estimated as accurate as possible. We conjecture the optimal solution is not very sensitive with respect to these cost figures considering the high cost of shortages. Nevertheless, for a fair benchmarking of two methods, exact figures are used where available. The slightly modified model of Arreola-Risa and DeCroix (1998) for our case is as follows:

$$\min_{\mathbf{S},\mathbf{s}} \quad \sum_{i=1}^{m} \mathrm{N}_i \left\{ \mathrm{k}_i + \mathrm{h}_i \left[\frac{\Delta_i}{\alpha_i} \left(\frac{\Delta_i + 1}{2} + s_i \right) + \frac{\beta_i}{\mu} \left(s_i - \frac{(1-\rho_i^{s_i})\alpha_i}{\mu_i} \right) \right] + \frac{\rho_i^{s_i}\beta_i\alpha_i\gamma_i}{\mu_i} \right\} \tag{3.13a}$$

$$\text{subject to} \quad \sum_{i=1}^{m} v_i S_i \leq V \tag{3.13b}$$

$$S_i = \Delta_i + s_i \tag{3.13c}$$

$$\Delta_i \geq \alpha_i \qquad i = 1, ..., m \tag{3.13d}$$

$$q_i = \lambda_{i'}/(\mu_{i'}+\lambda_{i'}) \qquad i = 1, ..., m \tag{3.13e}$$

$$s_i \geq 0 \qquad i = 1, ..., m, \tag{3.13f}$$

[1] If $\lambda_{i'} = 0$, then $q_i = 0$ no matter what the value of μ_i is, because the demand is never disrupted and the substitute is always available.

where

$$\beta_i = \frac{\lambda_i}{\lambda_i + \mu_i}\left[1 - \left(\frac{\alpha_i}{\alpha_i + \lambda_i + \mu_i}\right)^{\Delta_i}\right] \tag{3.14}$$

$$\rho_i = \frac{\alpha_i}{\alpha_i + \mu_i}, \tag{3.15}$$

$$\gamma_i = (1 - q_i)p_i + q_i\pi_i, \tag{3.16}$$

$$\mathrm{N}_i = \frac{\alpha_i\mu_i}{\mu_i\Delta_i + \alpha_i\beta_i}. \tag{3.17}$$

In this formulation, Δ_i is the order quantity as can be seen in constraint (3.13c). It should be noted that the model is capable of handling both unit backordering cost and backordering cost rate. We use unit backordering cost π_i rather than the rate, since one shortage does not cost with a constant rate over time. π_i are set to dollar amounts using the impacts in Table 3.2, as discussed in the previous model. Since the items share a common space, the total occupied space should not exceed the total warehouse capacity. Constraint (3.13b) ensures that warehouse capacity is not exceeded. Constraint (3.13d) provides a practical lower bound for order quantity so that an unrealistic output is not produced such as placing multiple orders in one day. As discussed earlier, constraint (3.13e) utilizes the substitute items' shortage and recovery rates. Finally, the objective function (3.13a) considers the sum of ordering cost, holding cost, and shortage cost. In this model, N_i will provide the long-run average number of orders placed per unit time for item i and β_i will provide the probability of finding the supply unavailable when the inventory level for item i hits s_i. The interested reader is referred to (Arreola-Risa and DeCroix, 1998) for details of the model and the derivation of the equations. In section 3.3.3, we present optimal inventory levels for the proposed models and simulation results to highlight the improvement over the current policy employed by a healthcare facility.

3.3.3 Computational Results

The healthcare facility we consider in this study is Harris County Hospital District (HCHD) in Houston, TX, which consists of a rehabilitation and specialty hospital, two full-service hospitals, 16 community health centers, seven school-based clinics, a dental and dialysis center, and mobile health units. HCHD participates in Disproportionate Share Hospital (DSH) programs, which is a special funding provided by the U.S. government for hospitals that treat significant populations of indigent patients. There are DSH programs for both Medicare and Medicaid, as well as for pharmacies, known as the 340B program. Inpatient pharmaceuticals are purchased through a wholesaler under an inpatient Group Purchasing Organization (GPO) account named Premier. Outpatient Pharmaceuticals are purchased through a wholesaler under Federal 340B Public Health Service (PHS) drug pricing program, which limits the cost of drugs to certain grantees of federal agencies. PHS pricing is subject to change quarterly. Participation in this program results in significant savings estimated to be 20% to 50% of the pharmaceuticals cost when compared with GPO pricing. The data provided by HCHD for critical items to be held in the warehouse is presented in Table 3.2. For privacy reasons, we do not present cost figures explicitly. Our results provide insights into the most efficient strategy for utilization of the 1200 ft^3 warehouse space reserved for these critical items.

In Table 3.2, the impact of shortages are estimated based on the QALYs of a patient without the drug and availability of alternative sources. Daily demand is obtained using the historical data. Disruption information is organized by the status of drugs (i.e., FDA approval, raw material availability, national shortages in the past) and pharmaeconomic expertise. Holding costs are calculated based on ordering cost and an annual interest rate for all items except those that require special handling or refrigeration requirements. Items that are relatively costly to hold are doxorubicin,

Item	Shortage Impact	Demand Rate (items/day)	Shortage Rate $\left(\frac{\text{shortages}}{\text{year}}\right)$	Exp(Shortage Duration) (months)	Volume (ft^3)
Furosemide	C	98.11	1	6	0.001
Bumetanide Inj	▲	▲	1	3	▲
Morphine	F	248	1	3	0.001
Hydromorphone Inj	▲	▲	1	1	▲
Levothyroxine	F	0.9	1	3	0.037
Liothyronine Inj	▲	▲	0	–	▲
Dipyridamole	G	8.7	2	3	0.008
Regadenosine	▲	▲	0	–	▲
Doxorubicin	E	4.22	1	7	0.125
Epirubicin	▲	▲	1	1	▲
Succinylcholine	D	46	1	6	0.001
Rocuronium	▲	▲	1	1	▲
Aminoacid	E	3.8	1	6	0.166
Premixed TPN	▲	▲	0	–	▲
Bleomycin	A	1	1	7	0.033
Cisplatin	B	2.38	1	6	0.125
Cytarabine	A	1.47	1	10	0.125
Etoposide Inj	A	3.77	1	7	0.008
Etoposide Oral	▲	▲	1	1	▲
Leucovorin Inj	A	5.1	2	9	0.008
Methotrexate Inj	B	3.63	2	3	0.166
Vincristine	B	2	1	6	0.033
Vinblastine	B	1.04	1	3	0.033
Asparaginase	F	0.06	1	3	0.037
Pegaspargase	▲	▲	1	6	▲
Mitomycin	C	0.5	2	3	0.037
Cyclophosphamide Inj	E	4.39	1	2	0.166
Fluorouracil	E	22.11	1	1	0.664
Capecitabine Inj	▲	▲	1	1	▲
Acetazolamide Inj	C	1.39	1	6	0.033
Acyclovir Inj	C	16.15	1	6	0.664
Alfentanyl Inj	G	2.22	1	2	0.125
Alprostadil Inj	C	0.27	1	6	0.037
Desmopressin Inj	E	4.27	1	3	0.166
Intralipids Inj	E	0.62	1	8	0.166
Folic Acid Inj	F	0.19	1	6	0.037
Fosphenytoin	C	28.25	2	4	0.664
Phenytoin Inj	▲	▲	2	3	▲
Norepinephrine	B	41	1	4	0.664
Propofol	D	152	1	6	0.664
Sulfamethoxazole/TMP Inj	F	12.78	1	4	0.664
Tromethamine Inj	F	0.22	1	4	0.125
Sodium Bicarbonate Inj	▲	▲	0	–	▲

Table 3.2: Parameters for critical items to be stored

succinylcholine, aminoacid, bleomycin, vincristine, vinblastine, asparaginase, and pegaspargase. Each row with ▲ sign corresponds to a substitute for the mainstream drug presented in the previous row, thus shortage impact, demand rate, and volume are the assumed same with the mainstream drug.

In order to evaluate the performance of different nonlinear programming formulations, General Algebraic Modeling System (GAMS) is used with CONOPT solver that is based on the extended cutting plane (ECP) method (GAMS, 2011). The input parameters are those in Table 3.2, where λ parameters are shortage rate column and μ parameters are reciprocals of expected shortage duration column. It is noteworthy that the modified model of Arreola-Risa and DeCroix (1998) took more time to solve

than the optimal reorder point model due to an increased number of decision variables and the structure of the objective function. Since the proposed models consider different objectives, Arena simulation software is used to compare different policies under the most realistic real-life scenario.

Table 3.3 presents the current policy, optimal solution of formulation (3.13), and optimal solution for formulation (3.70). The current policy does not utilize all available warehouse space as can be seen in the first column.

Item	**Current Strategy**		**Modified (s, S) Policy**		**Reorder Point Model**	
	Safety	Order Quantity	Safety	Order Quantity	Safety	Order Quantity
Furosemide Inj	125	125	79,761	98	29,859	98
Morphine Inj	1,700	2,300	46,725	248	10,945	248
Levothyroxine Inj	12	12	66	7	0	1
Dipyridamole	20	30	1381	14	0	9
Doxorubicin	20	30	0	8	0	4
Succinylcholine	25	25	26,951	63	4,776	46
Aminoacid	8	4	0	6	0	4
Bleomycin	15	15	679	6	810	1
Cisplatin	15	15	715	4	902	2
Cytarabine	20	20	776	2	1,197	1
Etoposide Inj	40	40	1667	11	298	4
Leucovorin Inj	30	30	6,789	7	7,961	5
Methotrexate Inj	10	20	681	4	594	4
Vincristine	20	20	1,083	5	1,245	2
Vinblastine	10	10	297	5	276	1
Asparaginase	5	5	2	2	0	1
Mitomycin	20	20	139	7	133	1
Cyclophosphamide Inj	15	15	130	11	0	4
Fluorouracil	10	10	0	22	0	22
Acetazolamide Inj	8	12	644	8	763	1
Acyclovir Inj	50	50	0	16	2	16
Alfentanyl Inj	10	10	0	2	0	2
Alprostadil Inj	10	10	119	3	143	1
Desmopressin Inj	10	10	170	8	71	4
Intralipids Inj	20	20	23	1	132	1
Folic Acid Inj	14	16	28	2	44	1
Fosphenytoin	100	100	0	28	0	28
Norepinephrine	20	30	485	41	591	41
Propofol	100	100	0	152	0	152
Sulfamethoxazole/TMP Inj	50	50	0	13	0	13
Tromethamine Inj	5	5	0	3	0	1

Table 3.3: Safety stock and order quantities for 3 different strategies

The simulation analysis is performed on a ten year time period. Simulation results for 10 replications for the current policy, modified (s, S) policy, and proposed reorder point model have been summarized in Tables 3.4 and 3.9.

Table 3.4 shows that the total number of shortages is the most with the current strategy, which is expected due to extremely low utilization of space. Our proposed

Item	Number of shortages		
	Current strategy	**Modified (s, S) Policy**	**Proposed Reorder Point Model**
Furosemide Inj	11,444	**0**	**0**
Morphine Inj	4,025	**0**	87
Levothyroxine Inj	**0**	**0**	**0**
Dipyridamole	**0**	**0**	**0**
Doxorubicin	200	**282**	290
Succinylcholine	4,790	**0**	**0**
Aminoacid	**0**	**0**	**0**
Bleomycin	723	**0**	**0**
Cisplatin	2,096	156	**77**
Cytarabine	1,926	144	**46**
Etoposide Inj	102	**0**	**0**
Leucovorin Inj	7,163	**0**	**0**
Methotrexate Inj	3,445	**249**	348
Vincristine	2,203	51	**35**
Vinblastine	610	**6**	8
Asparaginase	1	**4**	8
Mitomycin	190	**5**	7
Cyclophosphamide Inj	2,129	**1,317**	2,313
Fluorouracil	**617**	623	623
Acetazolamide Inj	1,356	66	**29**
Acyclovir Inj	15,041	15,536	**15,530**
Alfentanyl Inj	**963**	1,078	1,078
Alprostadil Inj	152	9	**4**
Desmopressin Inj	2,475	**1,417**	2,000
Intralipids Inj	561	601	**153**
Folic Acid Inj	114	93	**55**
Fosphenytoin	**6,317**	7,242	7,242
Norepinephrine	37,370	33,621	**32,832**
Propofol	**180,644**	181,224	181,224
Sulfamethoxazole/TMP Inj	**8,400**	8,838	8,838
Tromethamine Inj	0	0	0

Table 3.4: Average number of shortages for each item over 10 replications of 10 years for 3 different strategies

	Current strategy	**Modified (s, S) Policy**	**Proposed Reorder Point Model**
Shortage cost	\$1,384,282,500	\$1,116,322,500	\$1,112,140,500
Substitute cost	\$9,448,342	\$9,128,225	\$8,508,457
Ordering cost	\$9,319,650	\$6,878,720	\$8,617,103
Holding cost	\$41,417	\$638,498	\$353,568
Total cost	**\$1,403,091,908**	**\$1,132,967,943**	**\$1,129,619,628**

Table 3.5: Average costs over 10 replications of 10 years for 3 different strategies

reorder point model leads to a larger average number of shortages compared to the modified (s, S) policy, however, when impacts are considered these shortages cost less, as expected (see Table 3.9). Surprisingly, the proposed reorder point model also leads to less substitute and holding cost. We conjecture this is because of the relatively low demand of high impact items in this dataset, thus cannot be expected in general. It is also noteworthy from Table 3.9 that the proposed reorder point model is saving around \$300,000 more than the modified (s, S) policy annually, when shortage impacts

are matched with meaningful dollar costs. This is mainly due to the following reasons:

- For each highest impact drug (i.e., shortage impact of A), reorder point model has the same or less number of shortages compared to the modified (s, S) policy.
- For the second highest impact drugs (i.e., shortage impact of B), reorder point model has the same or less number of shortages compared to the modified (s, S) policy, except for Methotrexate Inj and Vinblastine, where there is a marginal difference. On the other hand, reorder point model is considerably better in Norepinephrine shortages.

Table 3.9 justifies disregarding other costs when shortages are present and have such a high impact, although these results are data dependent. Our proposed model aims to minimize solely the shortage cost, which is at least two orders of magnitude larger than other costs under real-life circumstances.

3.4 Second Solution Approach

This model is a more general form of the first model with less assumptions. The objective function of this model minimizes the total cost of the system. This model considers the order quantity as one of the decision variables and tries to find the optimal order quantity and safety stock level for each drug. In addition to the assumptions mentioned in Section 3.2, the proposed model in this preliminary work is considering the following assumption:

- An order for item i will be placed (i) when the inventory level hits reorder pointR_i and supply is available (regular reorder of size Q_i), (ii) if either one of the mainstream or substitute becomes unavailable when both were available (as a precaution), (iii) if either one of the mainstream or substitute becomes available, i.e., national shortage is over (as a recovery step). The orders are always placed to bring net inventory up to order-up-to level $Q_i + R_i$.

- Perishability of drugs has been considered by limiting the total inventory of each item proportional to its shelf life $\mathfrak{l}_i$.

3.4.1 Proposed Model

As we mentioned earlier, to solve this problem a stochastic approach using a continuous time Markov chain is proposed. In the light of assumptions in section 3.2, a Continuous Time Markov Chain is constructed as in Fig. 3.3.

In this transition-rate diagram, states are denoted as triplets where the first

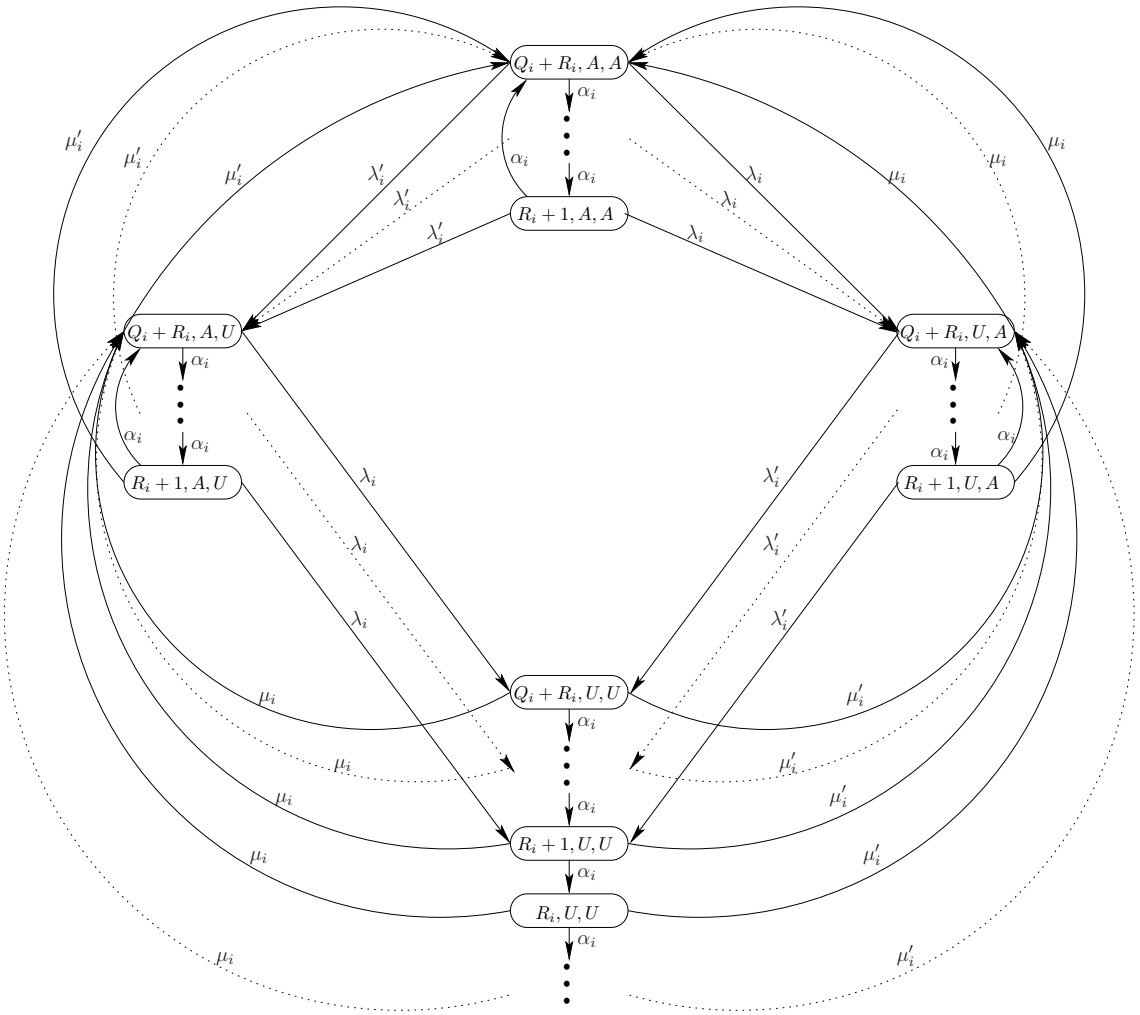

Figure 3.3: Transition-rate diagram for item i in the inventory system for the second model.

entry denotes the inventory level, the second and third entry denote the availability of the mainstream and substitute item, respectively. Note that, A denotes item is available, U denotes item is not available. α_i is the daily demand rate for the drug under consideration that may be mainstream drug or its substitute. λ_i and λ_i' denote the shortage rate for mainstream drug and it's substitute, respectively. Similarly, μ_i and μ_i' denote the shortage recovery rate of mainstream and substitute drugs, respectively. Next, we present a mathematical formulation to be solved to determine optimal reorder point and order quantity for each item.

α_i	Demand rate for drug i
λ_i	Supply disruption rate for drug i
μ_i	Rate of recovery from shortage for drug i
λ_i'	Supply disruption rate for substitute of drug i
μ_i'	Rate of recovery from shortage for substitute of drug i
$\mathfrak{l}_i$	Shelf life of drug i
π_i	shortage cost per drug i per year
π_i'	Substitution cost for drug i per year
h_i	Holding cost per drug i per year
v_i	Space occupied by drug i
V	Total warehouse capacity

Table 3.6: Proposed Model Parameters

In order to find the expected costs associated with this system, we first find the limiting probabilities using the transition-rate diagram in Fig. 3.3. First, we use the relationship between states that are grouped based on availability of a mainstream drug and its substitute. For example, when both the mainstream drug and its substitute are available (i.e., the set of states on top of Fig. 3.3), all limiting probabilities can be obtained in terms of $P_{Q+R,A,A}$ as follows:

$$P_{Q+R-j,A,A} = (\frac{\alpha}{\alpha+\lambda+\lambda'})^j P_{Q+R,A,A} \qquad j = 0, ..., Q-1, \tag{3.18}$$

Similarly, when the mainstream drug is unavailable and the substitute is available,

we obtain

$$P_{Q+R-j,U,A} = \Omega^j P_{Q+R,U,A} \qquad j = 0, ..., Q-1, \tag{3.19}$$

where $\Omega = \alpha/(\alpha + \mu + \lambda')$. When only the substitute drug is unavailable, the steady state probabilities are derived as

$$P_{Q+R-j,A,U} = \Omega'^j P_{Q+R,A,U} \qquad j = 0, ..., Q-1, \tag{3.20}$$

where $\Omega' = \dfrac{\alpha}{\alpha + \lambda + \mu'}$. Finally, when both the mainstream and substitute drugs are unavailable, we have

$$\begin{aligned} P_{Q+R-j,U,U} = {} & P_{Q+R,U,A}\left((\frac{\lambda'\alpha^j}{(\alpha+\mu+\mu')^{j+1}}) + \sum_{k=1}^{j}(\frac{\lambda'\alpha^{j-k}\Omega^k}{(\alpha+\mu+\mu')^{j-k+1}})\right) \\ & + P_{Q+R,A,U}\left((\frac{\lambda\alpha^j}{(\alpha+\mu+\mu')^{j+1}}) + \sum_{k=1}^{j}(\frac{\lambda\alpha^{j-k}\Omega'^k}{(\alpha+\mu+\mu')^{j-k+1}})\right) \qquad j = 1, ..., Q-1, \end{aligned} \tag{3.21}$$

$$P_{R-j,U,U} = P_{R+1,U,U}(\frac{\alpha}{\alpha+\mu+\mu'})^{j+1} \qquad j = 0, ..., \infty. \tag{3.22}$$

Using (3.18), we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = P_{Q+R,A,A}\left(\frac{1-(\frac{\alpha}{\alpha+\lambda+\lambda'})^Q}{1-(\frac{\alpha}{\alpha+\lambda+\lambda'})}\right), \tag{3.23}$$

and thus

$$P_{Q+R,A,A} = \frac{(\alpha+\lambda+\lambda')^{Q-1}(\lambda+\lambda')}{(\alpha+\lambda+\lambda')^Q - \alpha^Q} \sum_{k=R+1}^{Q+R} P_{k,A,A}. \tag{3.24}$$

Similarly, (3.19) and (3.20) can be used to obtain the following:

$$P_{Q+R,U,A} = \frac{(\alpha+\mu+\lambda')^{Q-1}(\mu+\lambda')}{(\alpha+\mu+\lambda')^Q - \alpha^Q} \sum_{k=R+1}^{Q+R} P_{k,U,A}, \tag{3.25}$$

$$P_{Q+R,A,U} = \frac{(\alpha+\lambda+\mu')^{Q-1}(\lambda+\mu')}{(\alpha+\lambda+\mu')^Q - \alpha^Q} \sum_{k=R+1}^{Q+R} P_{k,A,U}. \tag{3.26}$$

The limiting probability for state $Q+R, A, A$ can be written equating the rate at

which the process leaves and enters that state.

$$(\alpha+\lambda+\lambda')P_{Q+R,A,A} = \mu' \sum_{k=R+1}^{Q+R} P_{k,A,U} + \mu \sum_{k=R+1}^{Q+R} P_{k,U,A} + \alpha P_{R+1,A,A}, \tag{3.27}$$

We can rearrange terms and use equation (3.18) to obtain

$$P_{Q+R,A,A} = \frac{\mu'}{\alpha+\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\alpha+\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,U,A} + (\frac{\alpha}{\alpha+\lambda+\lambda'})^Q P_{Q+R,A,A}. \tag{3.28}$$

Adding $\sum_{k=R+1}^{Q+R-1} P_{k,A,A}$ on both sides, we have

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu'}{\alpha+\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\alpha+\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,U,A} + \sum_{j=1}^{Q} (\frac{\alpha}{\alpha+\lambda+\lambda'})^j P_{Q+R,A,A}, \tag{3.29}$$

because (3.18) implies

$$\sum_{k=R+1}^{Q+R-1} P_{k,A,A} = \sum_{j=1}^{Q-1} (\frac{\alpha}{\alpha+\lambda+\lambda'})^j P_{Q+R,A,A}. \tag{3.30}$$

Using properties of geometric series and (3.29), we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu'((\alpha+\lambda+\lambda')^Q - \alpha^Q)}{(\lambda+\lambda')((\alpha+\lambda+\lambda')^Q - \alpha^Q)} \sum_{k=R+1}^{Q+R} P_{k,A,U} \tag{3.31}$$

$$+ \frac{\mu((\alpha+\lambda+\lambda')^Q - \alpha^Q)}{(\lambda+\lambda')((\alpha+\lambda+\lambda')^Q - \alpha^Q)} \sum_{k=R+1}^{Q+R} P_{k,U,A}, \tag{3.32}$$

which can be simplified as

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu'}{\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\lambda+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,U,A}. \tag{3.33}$$

The limiting probability for state $Q+R,U,A$ can be obtained similar to $Q+R,A,A$.

First, the limiting probability is written as

$$(\alpha+\mu+\lambda')P_{Q+R,U,A} = \lambda \sum_{k=R+1}^{Q+R} P_{k,A,A} + \mu' \sum_{j=0}^{\infty} P_{Q+R-j,U,U} + \alpha P_{R+1,U,A}. \tag{3.34}$$

Next, $\sum_{k=R+1}^{Q+R-1} P_{k,U,A}$ is added on both sides and we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,U,A} = \frac{\lambda}{\mu+\lambda'} \sum_{k=R+1}^{Q+R} P_{k,A,A} + \frac{\mu'}{\mu+\lambda'} \sum_{j=0}^{\infty} P_{Q+R-j,U,U}. \tag{3.35}$$

Similarly, when the mainstream drug is available and the substitute is unavailable, we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,U} = \frac{\lambda'}{\mu'+\lambda} \sum_{k=R+1}^{Q+R} P_{k,A,A} + \frac{\mu}{\mu'+\lambda} \sum_{j=0}^{\infty} P_{Q+R-j,U,U}. \tag{3.36}$$

Using the fact that the summation of limiting probabilities for all states is 1, i.e.,

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} + \sum_{k=R+1}^{Q+R} P_{k,U,A} + \sum_{k=R+1}^{Q+R} P_{k,A,U} + \sum_{j=0}^{\infty} P_{Q+R-j,U,U} = 1, \tag{3.37}$$

and equations (3.33), (3.35) and (3.36) we have

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu\mu'}{(\mu+\lambda)(\mu'+\lambda')} \tag{3.38}$$

$$\sum_{k=R+1}^{Q+R} P_{k,A,U} = \frac{\mu\lambda'}{(\mu+\lambda)(\mu'+\lambda')} \tag{3.39}$$

$$\sum_{k=R+1}^{Q+R} P_{k,U,A} = \frac{\mu'\lambda}{(\mu+\lambda)(\mu'+\lambda')} \tag{3.40}$$

$$\sum_{j=0}^{\infty} P_{Q+R-j,U,U} = \frac{\lambda\lambda'}{(\mu+\lambda)(\mu'+\lambda')}. \tag{3.41}$$

Next, plugging (3.38), (3.39),(3.40), and (3.41) in (3.24), (3.25), and (3.26), steady state probabilities $P_{Q+R,A,A}$, $P_{Q+R,U,A}$ and $P_{Q+R,A,U}$ are found, which can be used to calculate all other steady state probabilities through (3.18), (3.19), and (3.20).

The states during unavailability of both the mainstream drug and its substitute can be divided into two groups for convenience. Using equation (3.21) we have

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \sum_{k=1}^{Q-1}\frac{\lambda'\alpha^{Q-k-1}\Omega^{k}}{(\alpha+\mu+\mu')^{Q-k}}\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \sum_{k=1}^{Q-1}\frac{\lambda\alpha^{Q-1-k}\Omega'^{k}}{(\alpha+\mu+\mu')^{Q-k}}\right), \tag{3.42}$$

which can be simplified as

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}}\sum_{k=1}^{Q-1}(\frac{\alpha+\mu+\mu'}{\alpha+\mu+\lambda'})^{k}\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}}\sum_{k=1}^{Q-1}(\frac{\alpha+\mu+\mu'}{\alpha+\lambda+\mu'})^{k}\right). \tag{3.43}$$

Using geometric series characteristics we obtain the following:

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}}(\frac{(\alpha+\mu+\lambda')^{Q}-(\alpha+\mu+\mu')^{Q}}{(\lambda'-\mu')(\alpha+\mu+\lambda')^{Q-1}}-1)\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}} + \frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^{Q}}(\frac{(\alpha+\lambda+\mu')^{Q}-(\alpha+\mu+\mu')^{Q}}{(\lambda-\mu)(\alpha+\mu'+\lambda)^{Q-1}}-1)\right). \tag{3.44}$$

Note again that $P_{Q+R,U,A}$ and $P_{Q+R,A,U}$ are obtained using equations (3.25, 3.40) and (3.26, 3.39), respectively.

3.4.2 Optimization Problem

In this model, the objective function that should be minimized is the expected annual total costs of the system which is the summation of expected shortage cost (SC), expected substitution cost (SubC) and expected holding cost (HC). Due to the specifics of healthcare sector described in the list of assumptions, there is no fixed ordering cost. Furthermore, variable ordering cost is billed directly to the patient because these facilities are operated on a non-profit basis. In this formulation π_i

denotes shortage cost per item i per year, π_i' denotes cost of substitution for each item i per year and h_i is holding cost per item i per year and the objective is to minimize $\sum_{i=1}^{m} TC_i(Q_i, R_i)$, where

$$TC_i(Q_i, R_i) = SC_i(Q_i, R_i) + SubC_i(Q_i, R_i) + HC_i(Q_i, R_i). \tag{3.45}$$

In this section, we explain the expected total cost for one item only ignoring index i for the sake of simplicity. Note that, shortage cost is charged when a state where both mainstream and substitute are unavailable is visited, independent from the time spent in these states. On the other hand, the holding cost is calculated considering the time spent in states using steady state probabilities directly. Thus, annual holding cost is

$$\begin{aligned} HC(Q,R) =& h(\sum_{j=0}^{Q-1}(Q+R-j)P_{Q+R-j,A,A} + \sum_{j=0}^{Q-1}(Q+R-j)P_{Q+R-j,A,U} \\ &+ \sum_{j=0}^{Q-1}(Q+R-j)P_{Q+R-j,U,A} + \sum_{j=0}^{Q+R}(Q+R-j)P_{Q+R-j,U,U}), \end{aligned} \tag{3.46}$$

which can be re-stated as

$$\begin{aligned} HC(Q,R) =& h(Q+R)(\sum_{j=0}^{Q-1} P_{Q+R-j,A,A} + \sum_{j=0}^{Q-1} P_{Q+R-j,A,U} + \sum_{j=0}^{Q-1} P_{Q+R-j,U,A}) \\ &- h(\sum_{j=0}^{Q-1} jP_{Q+R-j,A,A} + \sum_{j=0}^{Q-1} jP_{Q+R-j,A,U} \\ &+ \sum_{j=0}^{Q-1} jP_{Q+R-j,U,A} - \sum_{j=0}^{Q+R}(Q+R-j)P_{Q+R-j,U,U}), \end{aligned} \tag{3.47}$$

where

$$\sum_{j=1}^{Q-1} jP_{Q+R-j,A,A} = \frac{\alpha((\alpha+\lambda+\lambda')^Q - Q(\lambda+\lambda')\alpha^{Q-1} - \alpha^Q)}{(\lambda+\lambda')^2(\alpha+\lambda+\lambda')^{Q-1}} P_{Q+R,A,A} \tag{3.48}$$

$$\sum_{j=1}^{Q-1} jP_{Q+R-j,A,U} = \frac{\alpha((\alpha+\mu'+\lambda)^Q - Q(\mu'+\lambda)\alpha^{Q-1} - \alpha^Q)}{(\mu'+\lambda)^2(\alpha+\mu'+\lambda)^{Q-1}} P_{Q+R,A,U}, \tag{3.49}$$

$$\sum_{j=1}^{Q-1} jP_{Q+R-j,U,A} = \frac{\alpha((\alpha+\mu+\lambda')^Q - Q(\mu+\lambda')\alpha^{Q-1} - \alpha^Q)}{(\mu+\lambda')^2(\alpha+\mu+\lambda')^{Q-1}} P_{Q+R,U,A}, \tag{3.50}$$

$$\sum_{j=0}^{Q+R}(Q+R-j)P_{Q+R-j,U,U} = \sum_{j=0}^{Q-1}(Q+R-j)P_{Q+R-j,U,U} + \sum_{j=Q}^{Q+R}(Q+R-j)P_{Q+R-j,U,U}. \tag{3.51}$$

The second term in (3.51) can be calculated as follows:

$$\sum_{j=Q}^{Q+R}(Q+R-j)P_{Q+R-j,U,U} = \sum_{j=0}^{R}(R-j)P_R\left(\frac{\alpha}{\alpha+\mu+\mu'}\right)^j, \tag{3.52}$$

$$= P_R\left(\sum_{j=0}^{R} R\left(\frac{\alpha}{\alpha+\mu+\mu'}\right)^j - \sum_{j=0}^{R} j\left(\frac{\alpha}{\alpha+\mu+\mu'}\right)^j\right), \tag{3.53}$$

$$= P_R\left(R\left(\frac{(\alpha+\mu+\mu')^{R+1}-\alpha^{R+1}}{(\mu+\mu')(\alpha+\mu+\mu')^R}\right) - \left(\frac{\alpha(\alpha+\mu+\mu')((\alpha+\mu+\mu')^{R+1}-\alpha^R(R+1)(\alpha+\mu+\mu')+R\alpha)}{(\alpha+\mu+\mu')^{R+1}(\mu+\mu')^2}\right)\right). \tag{3.54}$$

We approximate the first term in (3.51) because the exact derivation is tedious.

$$\sum_{j=0}^{Q-1}(Q+R-j)P_{Q+R-j,U,U} \approx \frac{Q+1+2R}{2}\sum_{j=0}^{Q-1}P_{Q+R-j,U,U} = \frac{Q+1+2R}{2}(\sum_{j=0}^{\infty}P_{Q+R-j,U,U} - \sum_{j=-\infty}^{R}P_{j,U,U})$$

$$= \frac{Q+1+2R}{2}(\sum_{j=0}^{\infty}P_{Q+R-j,U,U} - P_{R,U,U}\frac{(\alpha+\mu+\mu')}{\mu+\mu'}). \tag{3.55}$$

Equations (3.41) and (3.44) can be plugged in (3.55) to provide necessary term for holding cost. Next, we calculate shortage and substitution costs using annual rate of visiting relevant states, which is either rate in or rate out. Shortage cost is obtained as:

$$SC(Q,R) = \pi(\alpha+\mu'+\mu)\sum_{j=1}^{\infty}P_{-j,U,U} = \pi P_{R+1,U,U}\frac{\alpha^{R+1}}{(\alpha+\mu+\mu')^R}\sum_{j=1}^{\infty}\left(\frac{\alpha}{\alpha+\mu+\mu'}\right)^j, \tag{3.56}$$

$$= \pi P_{R+1,U,U}\frac{\alpha^{R+1}}{(\alpha+\mu+\mu')^R}\left(\frac{\alpha}{\mu+\mu'}\right). \tag{3.57}$$

In order to find the rate of substitution, we find the rate of ordering for substitute items because the number of substitute items on hand do not diverge in the long

run. The rate of ordering for substitutes can be computed and multiplied by per unit substitution cost as follows:

$$SubC(Q,R) = \pi' \left(\alpha Q P_{R+1,U,A} + \lambda \sum_{j=1}^{Q-1} (Q-j) P_{R+j,A,A} + \mu' \sum_{j=1}^{Q+R} j P_{Q+R-j,U,U} + \mu'(Q+R) \sum_{j=1}^{\infty} P_{-j,U,U} \right). \tag{3.58}$$

Equations (3.19), (3.25), and (3.40) are used to obtain

$$P_{R+1,U,A} = \frac{\alpha^{Q-1}(\mu+\lambda')}{(\alpha+\mu+\lambda')^Q - \alpha^Q} \times \frac{\mu'\lambda}{(\mu+\lambda)(\mu'+\lambda')}. \tag{3.59}$$

For the second term, equation (3.18) is used to provide

$$\sum_{j=1}^{Q-1} (Q-j) P_{R+j,A,A} = P_{Q+R,A,A} \sum_{k=1}^{Q-1} k \left(\frac{\alpha}{\alpha+\lambda+\lambda'} \right)^k \tag{3.60}$$

$$= P_{Q+R,A,A} \frac{\alpha \left((\alpha+\lambda+\lambda')^Q - Q\alpha^{Q-1}(\alpha+\lambda+\lambda') + \alpha^Q(Q-1) \right)}{(\lambda+\lambda')^2 (\alpha+\lambda+\lambda')^{Q-1}}, \tag{3.61}$$

where $P_{Q+R,A,A}$ can be obtained using (3.24) and (3.38).

The third term can be separated to two parts:

$$\sum_{j=1}^{Q+R} j P_{Q+R-j,U,U} = \sum_{j=1}^{Q-1} j P_{Q+R-j,U,U} + \sum_{j=Q}^{Q+R} j P_{Q+R-j,U,U}. \tag{3.62}$$

The first part can be estimated as:

$$\sum_{j=1}^{Q-1} j P_{Q+R-j,U,U} \approx \frac{Q}{2} \sum_{j=1}^{Q-1} P_{Q+R-j,U,U} = \frac{Q}{2} (\sum_{j=0}^{Q-1} P_{Q+R-j,U,U} - P_{Q+R,U,U}), \tag{3.63}$$

$$= \frac{Q}{2} (\sum_{j=0}^{\infty} P_{Q+R-j,U,U} - \sum_{j=Q}^{\infty} P_{Q+R-j,U,U} - P_{Q+R,U,U}). \tag{3.64}$$

Using geometric series characteristics $\sum_{j=Q}^{\infty} P_{Q+R-j,U,U}$ can be calculated as

$$\sum_{j=Q}^{\infty} P_{Q+R-j,U,U} = P_{R+1}(\frac{\alpha}{\mu+\mu'}). \tag{3.65}$$

The steady state probability $P_{Q+R,U,U}$ can be simply calculated as:

$$P_{Q+R,U,U} = \frac{P_{Q+R,U,A}\lambda'}{\alpha+\mu+\mu'} + \frac{P_{Q+R,A,U}\lambda}{\alpha+\mu+\mu'}. \tag{3.66}$$

Equation (3.63) can be calculated plugging equations (3.65), (3.66) and (3.41) in it.

Second part can be written as:

$$\sum_{j=Q}^{Q+R} jP_{Q+R-j,U,U} = Q\sum_{j=Q}^{Q+R} P_{Q+R-j,U,U} + \sum_{j=Q}^{Q+R,U,U} (j-Q)P_{Q+R-j,U,U}, \tag{3.67}$$

$$= QP_{R+1,U,U}(\frac{\alpha}{\mu+\mu'})(1-(\frac{\alpha}{\alpha+\mu+\mu})^{R+1}) + P_{R+1,U,U}(\frac{\alpha}{\mu+\mu'})^2(1-\frac{\alpha^R(R+1)(\alpha+\mu+\mu')-R\alpha^{R+1}}{(\alpha+\mu+\mu')^{R+1}}). \tag{3.68}$$

Equation (3.67) can be calculated using equation (3.44).

Last term to be calculated is $\sum_{j=1}^{\infty} P_{-j,U,U}$, using equation (3.44).

$$\sum_{j=1}^{\infty} P_{-j,U,U} = P_{R+1,U,U}(\frac{\alpha}{\mu+\mu'})(\frac{\alpha}{\alpha+\mu+\mu'})^{R+1}. \tag{3.69}$$

Equations (3.59), (3.60), (3.62), (3.69) are plugged in (3.58) and derivation of substitute cost is complete.

The optimal reorder points for all items that minimize the expected annual cost

of the system can be obtained solving

$$\min_{\mathbf{R},\mathbf{Q}} \quad \sum_{i=1}^{m} TC(Q_i, R_i) \tag{3.70a}$$

$$\text{subject to} \quad \sum_{i=1}^{m} v_i \left[Q_i + R_i\right] \leq V \tag{3.70b}$$

$$ł_i \alpha_i \geq Q_i + R_i \qquad i = 1, ..., m, \tag{3.70c}$$

$$R_i \geq 0 \qquad i = 1, ..., m, \tag{3.70d}$$

$$Q_i \geq 0 \qquad i = 1, ..., m. \tag{3.70e}$$

The two constraints that have been considered in this model are capacitated warehouse (3.70b), and perishability constraints for drugs (3.70c). We ensure that the system under consideration never carries more than the expected demand to appear during the average lifetime of a drug. It should be noted that a more rigorous model that integrates perishability can also be studied by keeping track of dates for each drug on hand in a stochastic framework. However, based on our discussions with healthcare professionals, we agreed that it is an overcomplicated model that is virtually impossible to implement considering varying and inconsistent expiration dates in different batches and some of the current inventory management tools that disregard expiration dates for simplicity. Despite the fact that there is significant spoilage in some hospitals, it is the way inventory is controlled and the technology employed that has to change before proposing through models.

3.4.3 Solution Algorithm

When problem size increases, computation time for the formulation obtained in the previous section grows exponentially because it is a nonconvex optimization problem. In this section, a practical heuristic algorithm is proposed to solve the problem and find the near-optimal solution. The parameters used in our algorithm are as follows:

In order to construct the initial solution for our algorithm, the order quantity of

γ	Coefficient to construct the initial solution, e.g., initial order quantities are γ times the daily demand where $\gamma \geq 1$
θ	Number of critical items
β	Fraction of warehouse that is initially allocated to critical items

Table 3.7: Heuristic Algorithm Parameters

each item is fixed to γ times the daily demand. Assuming the orders are placed at least daily, γ can be any number greater than or equal to one since we need to order at least one day's demand. After assigning a portion of the warehouse to the order quantities, β percent of the remaining capacity of warehouse is assigned to θ *critical* items. Criticality of an item is roughly quantified based on demand rate, shortage cost per item, and shortage rate for both the mainstream and its substitute. Once the items are decided, warehouse capacity is distributed for safety stocks of these items based on their daily demand and volume. The idea is to allocate more space for larger items with higher daily demand. During this procedure, shelf lives of items are considered to make sure the assigned capacity is not expected to result in expired drugs. The remaining capacity of the warehouse will be assigned to the rest of the items (i.e., noncritical) in a similar fashion considering their daily demand and volume.

Next, we start with the initial solution and perform a neighborhood search. The neighborhood search includes two main steps, (1) removing the item that results in the minimum increase in the objective function per volume we free up, and (2) adding the item that results in the maximum decrease in the objective function per volume we occupy. The procedure continues until we observe no improvement in the objective function (3.70a). To provide uniformity in the removing procedure, the volume we free up and occupy is initially approximately the size of the largest item, which gradually decreases. Below is the detailed pseudocode of the algorithm and note that parameters are summarized in Tables 3.6 and 3.7.

Algorithm 1 Two-Phase Heuristic Algorithm

INPUT: $(\alpha_1, \ldots, \alpha_m)$, $(\lambda_1, \ldots, \lambda_m)$, $(\lambda'_1, \ldots, \lambda'_m)$, $(\mu_1, \ldots, \mu_m)$, $(\mu'_1, \ldots, \mu'_m)$, $(h_1, \ldots, h_m)$, $(\pi_1, \ldots, \pi_m)$, $(\pi'_1, \ldots, \pi'_m)$, $(v_1, \ldots, v_m)$, $(l_1, \ldots, l_m)$, $\mathbf{V}$, γ, θ, β

OUTPUT: $(R_1, \ldots, R_m)$, $(Q_1, \ldots, Q_m)$

{**Finding Initial Solution**}
$(Q_1, \ldots, Q_m) \leftarrow \gamma \times (\alpha_1, \ldots, \alpha_m)$
$V' \leftarrow V - \sum_{i=1}^{m} (v_i \times Q_i)$
if $V' < 0$ **then**
  Break
  {**No feasible solution with provided parameters**}
end if
$R_k \leftarrow \min \{l_k \alpha_k - Q_k, \frac{\beta \times V' \alpha_k v_k}{\theta \sum_{i=1}^{\theta} \alpha_i v_i}\}, \forall k \in 1, \ldots, \theta$
$R_k \leftarrow \min \{l_k \alpha_k - Q_k, \frac{(1-\beta) \times V' \alpha_k v_k}{(m-\theta) \sum_{i=\theta}^{m} \alpha_i v_i}\}, \forall k \in \theta, \ldots, m$
$t \leftarrow 1$
{**Neighborhood Search**}
while $GR_{i \in 1,\ldots,m} = 1$ **do**
  $GR_i \leftarrow \frac{max(v_i)}{v_i t}, \forall i \in 1, \ldots, m$
  $TC'(Q_i, R_i) \leftarrow \infty \; \forall i \in 1, \ldots, m$
  while $\sum_{i=1}^{m} TC'(Q_i, R_i) - \sum_{i=1}^{m} TC(Q_i, R_i) > 0$ **do**
    $TC'(Q_i, R_i) \leftarrow TC(Q_i, R_i) \; \forall i \in 1, \ldots, m$
    {**Removal of items**}
    for all $i \in 1, \ldots, m$ **do**
      $R'_i \leftarrow R_i - GR_i, \forall i \in 1, \ldots, m$
      $Q'_i \leftarrow Q_i - GR_i, \forall i \in 1, \ldots, m$
    end for
    $j \leftarrow argmin_{i \in 1,\ldots,m} \frac{TC(Q_i, R'_i) - TC(Q_i, R_i)}{v_i GR_i}$
    $k \leftarrow argmin_{i \in 1,\ldots,m} \frac{TC(Q'_i, R_i) - TC(Q_i, R_i)}{v_i GR_i}$
    if $\frac{TC(Q'_k, R_k) - TC(Q_k, R_k)}{v_k GR_k} < \frac{TC(Q_j, R'_j) - TC(Q_j, R_j)}{v_j GR_j}$ **then**
      $(Q_k, R_k) \leftarrow (Q'_k, R_k)$
    else
      $(Q_j, R_j) \leftarrow (Q_j, R'_j)$
    end if
    $V'' \leftarrow V - \sum_{i=1}^{m} v_i (Q_i + R_i)$
    {**Adding new items**}
    $GR'_i \leftarrow min \; \{l_i \alpha_i - Q_i - R_i, \; \frac{V''}{v_i}\}, \forall i \in 1, \ldots, m$
    for all $i \in 1, \ldots, m$ **do**
      $R''_i \leftarrow R_i + GR'_i, \forall i \in 1, \ldots, m$
      $Q''_i \leftarrow Q_i + GR'_i, \forall i \in 1, \ldots, m$
    end for
    $j' \leftarrow argmax_{i \in 1,\ldots,m} \frac{TC(Q_i, R_i) - TC(Q_i, R''_i)}{v_i GR'_i}$
    $k' \leftarrow argmax_{i \in 1,\ldots,m} \frac{TC(Q_i, R_i) - TC(Q''_i, R_i)}{v_i GR'_i}$
    if $\frac{TC(Q_{k'}, R_{k'}) - TC(Q''_{k'}, R_{k'})}{v_{k'} GR'_{k'}} > \frac{TC(Q_j, R'_j) - TC(Q_j, R_j)}{v_{j'} GR'_{j'}}$ **then**
      $(Q_{k'}, R_{k'}) \leftarrow (Q''_{k'}, R_{k'})$
    else
      $(Q_{j'}, R_{j'}) \leftarrow (Q_{j'}, R''_{j'})$
    end if
  end while
  $t \leftarrow 2t$
end while

3.4.4 Computational Results

Current inventory control strategies in two healthcare facilities (an anonymous hospital in Houston, TX and HCHD) and the result of the heuristic model are presented in Table 3.8. As shown in the table, resulting order quantity levels of the heuristic algorithm, regardless of the initial solution, are always close to one day of demand. In general, order quantities are set to the smallest possible value based on how deliveries are made.

Item	Anonymous Hospital's Strategy		HCHD's Strategy		Proposed Policy	
	Safety	Order Quantity	Safety	Order Quantity	Safety	Order Quantity
Furosemide	98	196	125	125	33,865	99
Morphine	248	496	1,700	2,300	20,121	248
Levothyroxine	1	2	12	12	0	1
Dipyridamole	9	18	20	30	0	9
Doxorubicin	4	8	20	30	3	5
Succinylcholine	46	92	25	25	4,717	46
Aminoacid	4	8	8	4	0	4
Bleomycin	1	2	15	15	359	1
Cisplatin	2	4	15	15	425	3
Cytarabine	1	2	20	20	262	2
Etoposide	4	8	40	40	428	4
Leucovorin	5	10	30	30	2,748	6
Methotrexate	4	8	10	20	710	4
Vincristine	2	4	20	20	358	2
Vinblastine	1	2	10	10	279	2
Asparaginase	1	2	5	5	0	1
Mitomycin	1	2	20	20	150	1
Cyclophosphamide	4	8	15	15	158	5
Fluorouracil	22	44	10	10	0	23
Acetazolamide	1	2	8	12	624	2
Acyclovir	16	32	50	50	0	17
Alfentanyl	2	4	10	10	0	3
Alprostadil	1	2	10	10	121	1
Desmopressin	4	8	10	10	208	5
Intralipids	1	2	20	20	37	1
Folic Acid	1	2	14	16	33	1
Fosphenytoin	28	56	100	100	34	29
Norepinephrine	41	82	20	30	857	41
Propofol	152	304	100	100	0	152
Sulfamethoxazole/TMP	13	26	50	50	0	13
Tromethamine	1	2	5	5	0	1

Table 3.8: Safety stock and order quantities for 3 different strategies

The expected costs for each strategy have been summarized in Table 3.9. It is noteworthy from Table 3.9 that the expected savings using the proposed model is more than $35,000,000 per year compared to current strategies, when shortage impacts are matched with meaningful dollar costs. The expected holding cost of the proposed

model, on the other hand, is higher than current strategies which do not utilize all available warehouse space.

	Anonymous Hospital's strategy	HCHD's strategy	Proposed Policy
Expected shortage cost	$ 158,702,574	$ 157,044,031	$ 121,423,566
Expected substitute cost	$ 7,018,190	$ 5,698,994	$ 3,951,208
Expected holding cost	$ 2,663	$ 3,352	$ 146,590
Expected total annual cost	**$ 165,723,427**	**$ 162,746,377**	**$ 125,521,374**

Table 3.9: Expected costs for 3 different strategies

Next, we focus on the solution provided by the heuristic algorithm via Table 3.10. In this table, items that have a substitute are presented bold. First column shows how many days of demand constitutes the safety stock. Drugs are listed in decreasing order of percentage of warehouse space allocated, which is presented in the second column. The last column in this table shows a soft measure for risk factor. It is the normalized value of multiplication of shortage impact, disruption rate and demand rate over the disruption recovery rate. The items that have a high shortage impact, high disruption rate, lengthy disruption duration (low recovery rate) and high demand rate have a higher risk factor value. In general, it is expected that (i) items with substitute occupy lower percentage of the warehouse, (ii) drugs with higher risk factor occupy higher percentage of the inventory space. This trend is generally observed in the table with a few exceptions:

- Although substitutes exist, some items occupy more space than expected because of the extremely high risk factors (e.g., Furosemide, Morphine).
- For some items, despite the relatively high risk factor, the percentage of the total space occupied is less that expected because they are relatively small items (e.g., Etoposide, Succinylcholine).
- Some items with substitutes and low risk factor occupy more space than expected because of their large volume (e.g., Foshphenytoin, Fluorouracil).

Because there are a number of attributes for each item that affect the total expected cost, we do not expect a simple ordering of items based on one measure. However, a pairwise comparison reveals the reasoning behind the safety stock and order quantity levels. If the total space was assigned uniformly to all items, each should be allocated approximately 3% of the total warehouse space. However, for example, Norepinephrine occupies almost half of the warehouse space. This is because of the large volume — even though most of the warehouse is used, safety stock provides only 21 days of demand. Despite the capacity occupied by Norepinephrine, the number of days safety stock for Norepinephrine would suffice is the lowest among drugs with a shortage impact of B. Likewise, items that appear higher than expected on the list due to large volume such as Foshphenytoin and Fluorouracil can suffice no more than a day.

3.5 Sensitivity Analysis

In this section, we present sensitivity analysis results to evaluate the effect of variations in input parameters such as disruption types and capacity on the expected total cost. Sensitivity analysis is performed for three group of input parameters: heuristic algorithm parameters, disruption related parameters, and warehouse capacity.

First group of the parameters are heuristic algorithm parameters used in constructing the initial solution. Table 3.11 shows the result of the heuristic algorithm under different values for θ, γ, and β. The convergence of the objective function for the parameters that result in the best and worst objective function values are presented in Fig. 3.4. The results show that (i) the second phase of the heuristic algorithm works pretty well improving the objective function value drastically, (ii) proposed neighborhood search is sensitive to the initial solution, and (iii) regardless of the values of input parameters, the objective function converges to a decent quality solution.

Second group of parameters are the rate of disruption and the rate of recovery from

Item	# of days safety stock would suffice (R_i/α_i)	Percentage of total space	Risk factor
Norepinephrine	21	49.689	0.000629
Methotrexate	196	9.877	0.000334
Propofol	0	8.411	0.001867
Cisplatin	179	4.458	0.000291
Fosphenytoin	1	3.486	0.000578
Desmopressin	49	2.947	0.000066
Furosemide	345	2.83	1
Cytarabine	178	2.75	0.0004
Cyclophosphamide	36	2.255	0.000045
Leucovorin	539	1.836	0.038987
Acetazolamide	449	1.722	0.000429
Morphine	81	1.697	0.252777
Fluorouracil	0	1.273	0.000028
Bleomycin	359	0.99	0.000721
Vincristine	179	0.99	0.000927
Acyclovir	0	0.941	0.000248
Vinblastine	268	0.773	0.000241
Sulfamethoxazole/TMP	0	0.719	0.000026
Intralipids	60	0.526	0.000025
Mitomycin	300	0.466	0.000138
Succinylcholine	103	0.397	0.375089
Alprostadil	448	0.376	0.000074
Etoposide	114	0.288	0.011208
Folic Acid	174	0.105	0.00001
Doxorubicin	1	0.083	0.000201
Aminoacid	0	0.055	0.00014
Alfentanyl	0	0.031	0.000006
Tromethamine	0	0.01	0.000002
Dipyridamole	0	0.006	0.001108
Levothyroxine	0	0.003	0.000025
Asparaginase	0	0.003	0.000002

Table 3.10: Ratio of the safety stock to the daily demand, percentage of the warehouse allocated to each item and shortage impact of each item

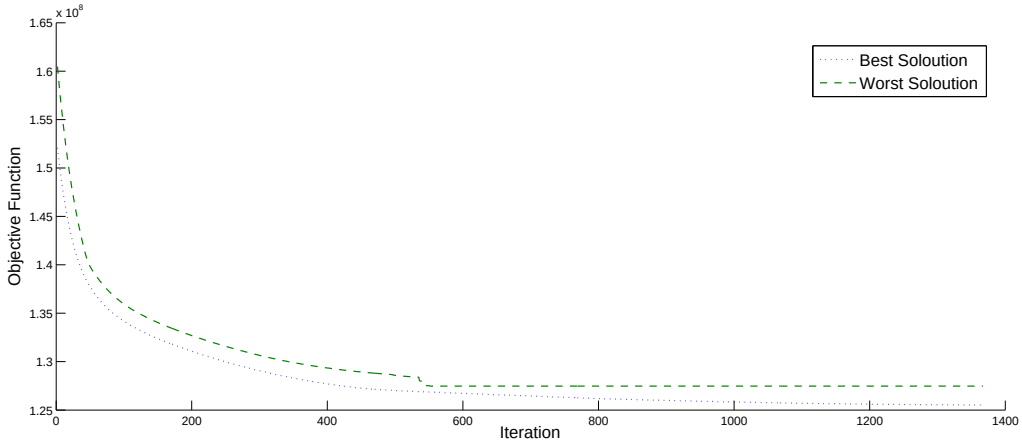

Figure 3.4: Convergence of objective function for best solution ($\theta = 10, \gamma = 1,\ \beta = 0.4$) and worst solution ($\theta = 10, \gamma = 3,\ \beta = 0.6$)

θ	β \ γ	**1**	**2**	**3**	**4**	**5**	**6**
0%	**0%**	127,083,672	125,554,428	125,644,742	125,557,192	125,559,570	125,562,832
5%	**20%**	125,529,524	Infeasible	Infeasible	Infeasible	Infeasible	Infeasible
	40%	127,034,870	125,533,250	125,824,120	Infeasible	Infeasible	Infeasible
	60%	127,412,136	125,626,351	125,544,110	125,556,194	125,602,362	Infeasible
	80%	127,071,188	125,546,000	125,546,326	125,543,176	125,595,255	Infeasible
10%	20%	125,526,867	Infeasible	Infeasible	Infeasible	Infeasible	Infeasible
	40%	125,519,170	125,531,578	125,542,079	Infeasible	Infeasible	Infeasible
	60%	125,525,914	125,533,323	127,470,121	125,558,791	Infeasible	Infeasible
	80%	127,469,498	125,536,069	125,562,350	125,559,029	125,560,366	125,563,278
15%	**20%**	125,526,961	Infeasible	Infeasible	Infeasible	Infeasible	Infeasible
	40%	125,535,323	125,523,628	125,534,237	Infeasible	Infeasible	Infeasible
	60%	125,525,841	125,539,181	125,633,374	125,708,020	infeasible	Infeasible
	80%	125,571,032	125,568,937	125,561,715	125,561,212	125,556,658	125,563,306

Table 3.11: Sensitivity analysis results for parameters of heuristic algorithm (θ, γ, β)

disruption. For this set of experiments we set θ, γ, and β to the values that provide the best solution above (i.e., $\theta = 10, \gamma = 1$, and $\beta = 0.4$). The input parameters are those in Table 3.2, where λ is the disruption rate and μ is the reciprocal of the expected disruption duration. In Fig. 3.5, we present the effect of frequency of disruptions on the total cost. ζ is the coefficient of increase or decrease for disruption rates (λ). In other words, the disruption rate for each item, regardless of being mainstream or substitute, is multiplied by ζ. As it is shown, increasing the rate of disruption will cause almost a linear increase in the expected total cost so objective function is highly sensitive to changes on the disruption rate.

Fig. 3.6 represents the changes in disruption and recovery rate simultaneously. In this figure, ζ' corresponds to the multiplier for both disruption and recovery rate, i.e., the new disruption rate for item i is $\zeta' \times \lambda_i$ and its recovery rate from disruption is $\zeta' \times \mu_i$. As shown in the figure, if supplies are unavailable more frequently but the unavailability duration decreases, the expected total cost will decrease. Despite the fact that the long-run fraction of supply unavailability stays the same, shorter and more frequent supply unavailability periods give the hospital a better opportunity for

recovery.

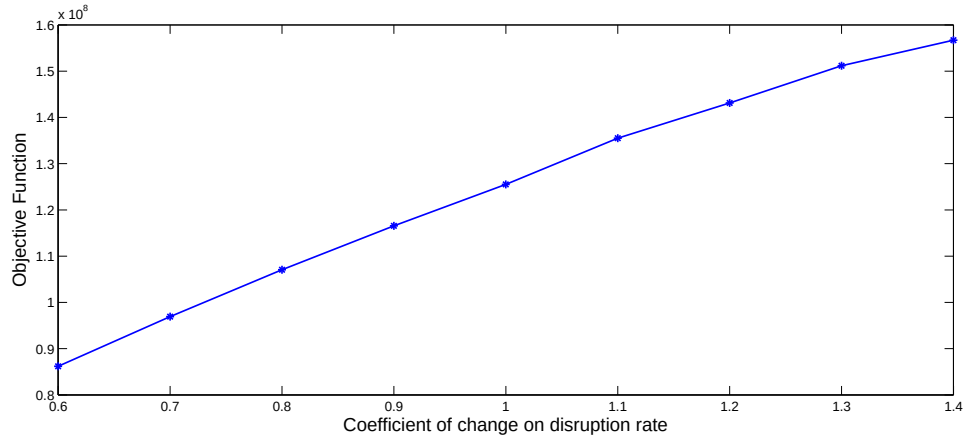

Figure 3.5: Sensitivity analysis on supply disruption multiplier (ζ). New disruption rate for items, regardless of being mainstream or substitute, is multiplied by ζ. ($\theta = 10, \gamma = 1$, $\beta = 0.4$)

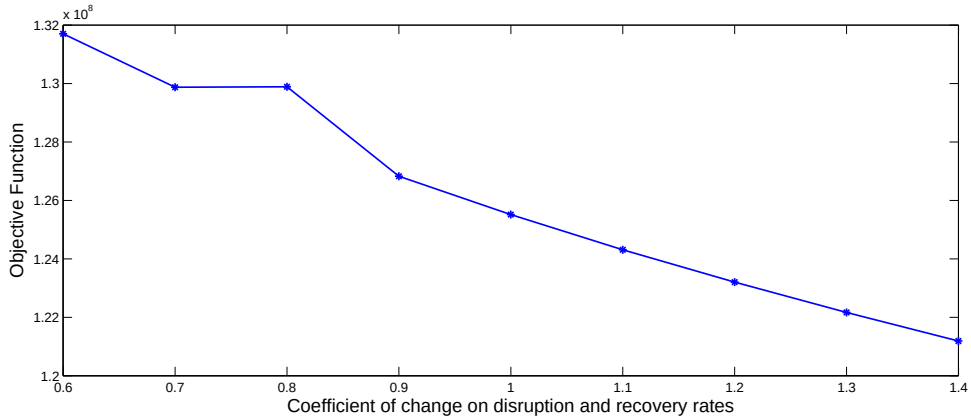

Figure 3.6: Sensitivity analysis on supply disruption and recovery rate multiplier ζ'. New disruption and recovery rates for items, regardless of being mainstream or substitute, is multiplied by ζ'. ($\theta = 10, \gamma = 1$, $\beta = 0.4$)

The last input parameter that we analyze is the total warehouse capacity. Fig. 3.7 shows, as it is expected, increasing the total capacity leads to a decrease in expected total cost. It should be noted that no cost improvement is observed beyond a certain value (for our data $\approx 55,000$ ft^3). A further increase in capacity beyond this point provides only a marginal decrease in the expected shortage cost but increases the holding cost as well. Another interesting observation is that the runtime of our

algorithm increases with increased warehouse space because of the number of feasible solutions (see Fig. 3.8). However, in the case of space abundance (beyond $\approx 55,000$ ft^3), the runtime decreases drastically because the quality of the initial solutions. As expected, increased space solves major drawbacks of national shortages to a certain extent. The practical implementation of this might be inventory pooling. A vast majority of the problems arising with national drug shortages can be alleviated via inventory pooling between hospitals. That available warehouse space, if managed well, will help reduce shortages as presented here and balance the variation in uncertain demand among different healthcare facilities as well.

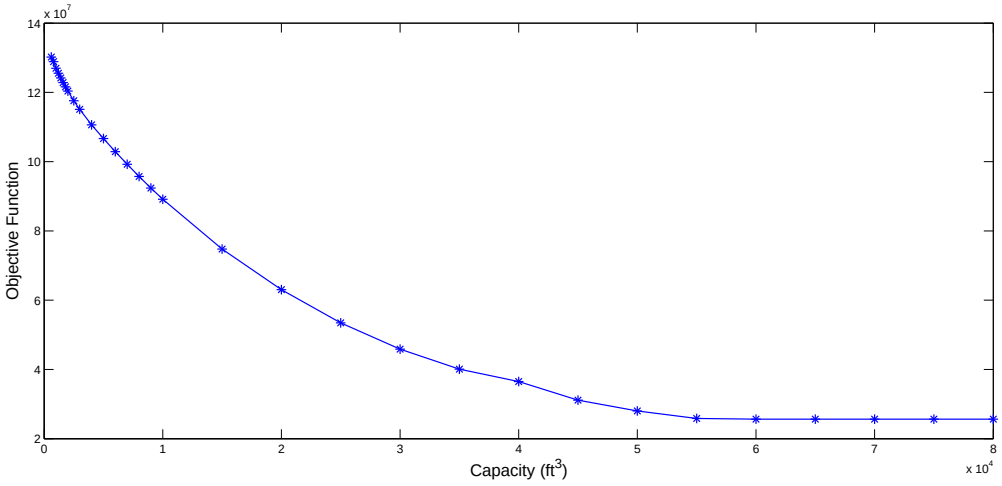

Figure 3.7: Sensitivity analysis on total inventory space ($\theta = 10, \gamma = 1, \beta = 0.6$)

3.6 Concluding Remarks

The main goal of this section is to present a framework for a healthcare facility to cope with inevitable supply disruptions. The more crucial an item is, the more safety stock is expected to be held. We present two stochastic optimization framework to find the optimal inventory management strategy. First model minimizes the shortage cost while finding the best safety stock levels. Simulating the results of this model and comparing them by current strategies, proposed model will save considerable amount

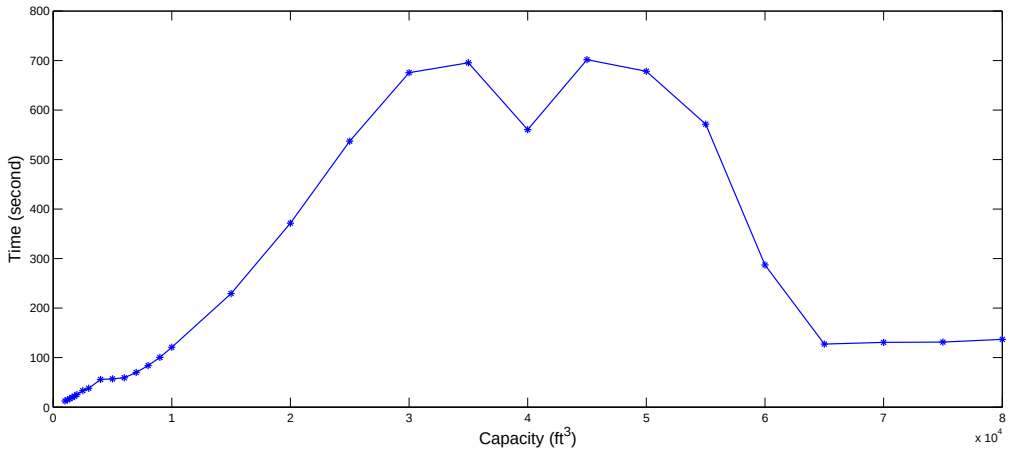

Figure 3.8: Time analysis for different inventory spaces ($\theta = 10, \gamma = 1, \beta = 0.4$)

of costs. The second stochastic model is proposed to define the optimal safety stock levels and order quantity levels that minimize the total cost, thus effect of supply disruptions. This model considers shelf life of the drugs as a constraint.

Conventional models consider the tradeoff between different costs of an item and achieving an optimal solution even in the case of unlimited capacity. What makes pharmaceutical supply chains unique is a set of attributes such as zero lead time, zero fixed-cost ordering, supply disruption, item substitution, and importance of service levels, implying a high warehouse utilization independent from the size. Therefore, we seek to find the balance point between items, considering the space occupied by an item, disruption rates, expected duration of a disruption (i.e., recovery rate), demand rate, as well as substitute item's disruption rate and duration. The results show that the proposed scheme is better compared to the current policies in all aspects of the inventory in a healthcare facility except for the holding cost, which is expected due to the currently low utilization of space.

Substitute items often cost more than mainstream drugs and may go short, however no model in the literature, to the best of our knowledge, utilizes that information. We assume that some of the drugs have substitutes and if they are available substitution can be performed with some cost. An interesting immediate extension of the

model would be considering items with more than one substitute. Furthermore, there is a *quality of service* aspect related to substitutes. A substitute may not be as effective as a mainstream drug for all patients. Some substitutes may not be preferred agents although they might be less expensive such as sodium bicarbonate (substituting tromethamine) or capecitabine (substituting fluorouracil). A multi-criteria framework can consider the total cost similar to a conventional inventory model on one dimension and the quality of service that assesses the impacts of shortage and substitution on another. Rather than one optimal solution, a set of solutions on the efficient frontier can be further evaluated under different conditions. In current study the shelf life of drugs is assumed to a deterministic value. Another possible branch to extend current work is considering the shelf life of each item probabilistic which will add another source of stochasticity to the model.

Chapter 4

A Game Theoretical Approach for Inventory Sharing

This chapter addresses inventory sharing as an advantageous strategy for hospitals during a drug shortage. In this chapter a game theoric approach has been used to suggest a strategy for inventory sharing during a drug shortage and analyze the interactions among hospitals in this collaboration.

4.1 Background and Literature Review

Evidence shows that, like many elements of the drug shortage problem, the response to these shortages is both hospital/pharmacy dependent, and somewhat ad-hoc. Among the most popular options for healthcare providers in immediate need is either (i) transaction from secondary supplier or (ii) trade/borrow from other healthcare providers (Young, 2009). Such practices have been reported as recently as February 2011 between the University of Chicago Medical Center and Chicago-area hospitals (Rubin, 2011).

Information from our partnering hospital in Houston, TX suggests that hospitals would have interest in exploring the option of considering efforts that allow the determination of a hospital's inventory to be, perhaps in part, determined in conjunction with partnering healthcare facilities. Other evidence of interest in this area is seen through separate work that represents aggregate inventories via a virtual pharmacy inventory system for hospitals in the same geographical region (Danas et al., 2006). This visual tool does strives to provide the infrastructure for the cooperation of hospital pharmacies. This is particularly relevant to the proposed work, since the concept of inventory sharing is familiar to healthcare providers and data for decision tools is

available via systems such as the virtual pharmacy. In this section, *we propose to complete the first preemptive modeling for combating pharmaceutical drug shortage by approaching the problem from a game theoric point-of-view.*

When there is a decision making problem with multiple decision makers with 1 objective each, a game is forming. Decision makers are called the players, decision alternatives are called the strategies and objective functions are called the payoff functions. Game theory models can be roughly divided into two groups, cooperative and non-cooperative, based on interdependence among the players. Non-cooperative game theory assumes that the goal of each player in the game is to optimize its own objective ignoring the effect of its decisions on other players. The goal in these models is finding optimal strategies for each player. Binding agreements among the players are not allowed. The existing coordination mechanisms or strategies that coordinate the supply chain in reality to maximize the total joint profit of the firms, is one of the main concerns when applying cooperative game theory for supply chains.

On the other hand, cooperative game theory models assume that players can make binding agreements. In these models the focus is on which coalition of players will form and which allocation of the joint worth will be used. This concept was first introduced by Von Neumann and Morgenstern (1944) with coalitional games in characteristic function form, known as transferable utility games (TU-games). Inventory centralization or inventory sharing, one of the important aspects of supply chain collaboration, has been studied using a cooperative game theory approach. The main reason for using cooperative games is developing a framework across structurally different inventory centralization models to determine the effect of coordinated ordering/holding by retailers, which results in joint worth (benefit or cost). The first main concern in these models is finding a stable allocation of worth such that no group of players can do better on its own and tends to leave the coalition. If such an allocation exists, the core of the game is not empty, or in other words the coalition is

stable (Meca and Timmer, 2007). The set of cost allocations, under which no group of players should be charged more than they would pay if they were separate and follow an optimal strategy for themselves, is called core. Second main question in a cooperative inventory game is identifying an allocation in the core which is usually challenging. It is shown that even in a very simple setting, determining whether an allocation is in the core of the newsvendor game is NP-hard (Chen and Zhang, 2009).

Benefits of inventory sharing, which are decreasing costs and increasing profits, have been shown in different inventory problems (Eppen, 1979), (Eppen and Schrage, 1981), (Chen and Lin, 1989) and (Chang and Lin, 1991). These early studies assume single ownership of the system while in real world problems players are interested in what they gain from inventory sharing.

The literature of Inventory centralization can be roughly divided into two sections: cooperation in deterministic inventory situation and cooperation in stochastic inventory situation. Cooperation under deterministic situation was studied for the first time by Meca et al. (2003) in which the SOC rule (Share the Ordering Costs) is introduced and defined as a core allocation for inventory cost games. Extension of this work has been done in (Meca et al., 2004), (Dror and Hartman, 2007) and (Mosquera et al., 2008).

The focus of most of the papers in centralization under non-deterministic situations is on the Newsvendor problem. These models often assume complete pooling of inventory. In complete pooling of inventory, inventory is diverted to satisfy demand that creates the highest profit from any stock point. The Newsvendor centralization game has been first presented by Hartman (1994). Hartman et al. (2000) studied identical newsvendors with normally distributed demand and proved the core of the game is not empty. Müller et al. (2002) generalizes this result for all possible distributions of demand. An extension of this work for an infinite number of players is done in (Montrucchio and Scarsini, 2007). While in these models the newsvendor game is a

cost game, Slikker et al. (2005) transform it into profit game by adding transshipment to model. In their model, stores do transshipment after demand realization. They also prove that newsvendor games with transshipments have a non-empty core even if the stores have different retail and wholesale prices. Also in general newsvendor games are not concave. An extension of this work has been done by Özen et al. (2008). In their model the original orders are kept in warehouse and shipment to retailers takes place after demand realization. Another study of the Slikker et al. (2005) and Özen et al. (2008)'s games is introduced in (Chen and Zhang, 2009). In this model a unified approach using stochastic programming and strong duality of stochastic linear programming is presented to examine the game. This approach proves the non-emptiness of the game, and also suggests a way to find a core-allocation. An adaptation of this work is introduced to analyze the inventory centralization game with price-dependent demand and quantity discounts (Chen, 2009). This is the first work considering pricing decisions for inventory centralization games.

Another group of studies with more restrictive setting and no complete pooling was first introduced by Anupindi et al. (2001). In their model, the retailers keep local inventory and after satisfying their local demand, they cooperate by transshipping excess inventory to satisfy excess demand in other locations. This work has been extended by Granot and SoŠić (2003) by considering an intermediate stage in which the retailers decide how much of their excess inventory/demand they want to share with others. Further extension of later work has been done by Sošić (2006). Ozen et al. (2012) assume that the retailers invest in a common pool of inventory but they impose some level of stock that should be dedicated to them. They prove the associated cooperative game has a non-empty core.

Most of the aforementioned studies prove the non-emptiness of core but they do not determine an allocation in the core except (Montrucchio and Scarsini, 2007) and (Chen and Zhang, 2009). Montrucchio and Scarsini (2007) prove that the core of a

simple newsvendor game is non-empty by identifying a core element. Chen and Zhang (2009) introduce an approach using strong duality of stochastic linear programs to identify core elements. Although this study used the model by Özen et al. (2008), it can be applied to a broad class of cooperative games arising from inventory sharing. Considering the compatibility of the assumptions of this model with pharmaceutical inventory sharing, a modified version of it can be used to handle pharmaceutical inventory sharing.

4.2 Problem Statement

As discussed earlier in Section 1.2 and 4.1, one of the possible approaches for facing shortages is inventory sharing among hospitals and it can be approached using a cooperative game theory structure. The main goal in a collaboration is minimizing the cost or maximizing the benefit of the collaborators in a way that they can't do better on their own. Considering the high impact of shortages in the service level of a hospital, in a hospital inventory sharing setting, a hospital will stay in collaboration if the expected value of the number of items that it receives from other hospitals during the shortage period is more than zero. On the other hand, when demand of the hospital is less than its inventory level, it can share its extra inventory with other hospitals and minimize its holding cost. Before a hospital joins a collaboration two main questions arise: (i) Whether the benefit is more in collaboration? (ii) Which hospitals are better choice in an inventory sharing? To answer these two questions the model for the collaborative game among hospitals is developed in section 4.3 and synergy of sharing among hospitals is analyzed in section 4.4.

4.3 Proposed Model

In this section using two stage stochastic programming and game theoric approach, introduced by Chen and Zhang (2009), a near optimal strategy for the inventory sharing problem between a set of pharmacies is suggested. Chen and Zhang (2009) have proved nonemptiness of the core of this game. Therefore solving the model results in an optimal strategy for cooperation among hospitals.

The proposed model considers the following assumptions:

- System consists of a supplier and a set of n pharmacies denoted by $N = 1, 2, ..., n$ with an associated warehouse.
- The supplier supplies a single type of drug.
- The pharmacies may face supply disruption. The rate of recovery from supply disruption is μ and it follows exponential distribution. The pharmacies will be informed about an upcoming disruption right before disruption happens.
- Each pharmacy $j \in N$ faces random demand $d_j(\omega)$.
- When a subset $S \subset N$ of pharmacies forms a coalition, then any pharmacy in S can borrow items from other pharmacies in coalition.
- For any coalition S, $d^S(\omega) = (d_j(\omega))_{j \in S}$ and when the demand of pharmacy j is realized $d^S = (d_j)_{j \in S}$.
- Since we are considering the period of disruption as a single period, the lead time is assumed zero without loss of generality.

The problem has been modeled using two stage stochastic programming. In the first stage, pharmacy j will order y_j units of drug with ordering cost of c_j per item. The first stage decision variable is y_j. In this stage demand at each pharmacy and the length of shortage period is unknown.

In second stage, the demands for each pharmacy and length of shortage period

is realized. Then, the available drugs are allocated to the pharmacies. x_{ij} units of drug are shipped from warehouse of pharmacy i to pharmacy j. The transportation cost of sending one unit of drug from i to j is s_{ij}. However, the cost of sending drugs from warehouse of pharmacy j to pharmacy j is zero. The unsatisfied demands in pharmacy j have a direct effect on patients' health so the pharmacy should pay a per-unit penalty cost of π_j for each shortage. If pharmacy j has z_j unsatisfied demand, the shortage cost for it will be $\pi_j z_j$ for whole shortage period. The holding cost for shortage period for each item at pharmacy j is h_j. Without loss of generality, it can be assumed that the average number of items in the warehouse of pharmacy j during shortage period is half the summation of the inventory level at beginning of the period, y_j, and excess inventory at the end of the period, I_j. All parameters and variables used in the model are summarized in Table 4.1.

ω	Demand scenario during shortage
c_i	Ordering cost per item in hospital i
π_i	Penalty cost of shortage per item in hospital i
h_i	Holding cost per item for hospital i
s_{ij}	Transportation cost per item fromhospital i to hospital j

Table 4.1: Cooperation Model Parameters

The goal in this problem is minimizing the expected total cost of coalition, $C(S)$. It includes the ordering cost, transportation cost, inventory holding cost, and penalty cost. It can be formulated as following two stage stochastic programming,

$$C(S) = \min_{y_i} \quad \sum_{i \in S} c_i y_i + E[f(y, d^S(\omega))] \tag{4.1a}$$

$$\text{s.t.} y_i \geq 0, \qquad i \in S, \tag{4.1b}$$

where $y = (y_i)_{i \in S}$ and, and $f(y, d^S)$ is shown as

$$f(y, d^S) := \min_{\mathbf{x_{ij}}} \quad \sum_{j \in S} \pi_j z_j + \sum_{j \in S} h_j \frac{y_j + I_j}{2} + \sum_{j \in S} s_{ij} x_{ij} \tag{4.2a}$$

$$\text{s.t.} \quad z_j + \sum_{i \in S} x_{ij} \geq d_j \qquad j \in S, \tag{4.2b}$$

$$I_j - \sum_{i \in S} x_{ij} \geq -d_j \qquad j \in S, \tag{4.2c}$$

$$y_i - \sum_{j \in S} x_{ij} = 0 \qquad i \in S, \tag{4.2d}$$

$$z_j, I_j, x_{ij} \geq 0. \tag{4.2e}$$

In second stage formulation, the first constraint implies that the unsatisfied demand is a lost patient. The second constraint shows that the summation of received drugs at each pharmacy should not exceed the summation of demand and excess inventory and the third constraint implies that the warehouses will be empty at the end of the period. This constraint is for ease of presentation. Using an auxiliary pharmacy attached to each warehouse with zero demand and zero transportation cost from the associated warehouse, without loss of generality it can be assumed that the warehouse do not hold any inventory at the end.

To solve a two-stage stochastic linear programming problem, it can be reformulated as a deterministic equivalent problem which is a large scale problem. Considering discrete distribution of demand, negative binomial, we can formulate the recourse function or expected second-stage value function as:

$$E[f(y, d^S(\omega))] = \sum_{d^S(\omega) \in \Omega} p(d^S(\omega)) f(y, d^S(\omega)). \tag{4.3}$$

In which Ω is the set of all possible demand scenarios during the shortage period.

Using equation (4.3), deterministic equivalent of the model is as follow:

$$C(S) = \min_{y_i} \quad \sum_{i \in S} c_i y_i + \sum_{\Omega} p(\omega)(\sum_{j \in S} \pi_j z_j^\omega + h_j \frac{y_j + I_j^\omega}{2} + s_{ij} x_{ij}^\omega) \tag{4.4a}$$

$$\text{s.t.} \quad z_j^\omega + \sum_{i \in S} x_{ij}^\omega \geq d_j^\omega \qquad j \in S, \tag{4.4b}$$

$$I_j^\omega - \sum_{i \in S} x_{ij}^\omega \geq -d_j^\omega \qquad j \in S, \tag{4.4c}$$

$$y_i - \sum_{j \in S} x_{ij}^\omega = 0 \qquad i \in S, \tag{4.4d}$$

$$y_i \geq 0, \qquad i \in S, \tag{4.4e}$$

$$z_j^\omega, I_j^\omega, x_{ij}^\omega \geq 0. \tag{4.4f}$$

To solve the deterministic equivalant of the model, possible demand scenarios should be identified. Each pharmacy $j \in N$ faces random demand $d_j(\omega)$. It is assumed earlier in section 3.2 that daily demand, d_{daily}, follows Poisson distribution with rate α. Considering the characteristics of Poisson distribution, summation of independent Poisson random variables is Poisson. Therefore, assuming demand at each day is independent from other days, demand during y days of shortage, $d_{shortage}$, follows Poisson distribution with parameter αy. It is known that the length of shortage, y, is stochastic and follows exponential distribution with rate μ. Therefore we have the following inputs:

$$d_{daily} \sim Poisson(\alpha), \tag{4.5a}$$

$$d_{shortage} \sim Poisson(\alpha y), \tag{4.5b}$$

$$y \sim Expo(\mu). \tag{4.5c}$$

We need to find distribution of αy to use compound distributions and find the distribution of demand. To find the distribution of αy, the moment generation function

of it is calculated as:

$$E[e^{t\alpha y}] = \int_0^\infty e^{t\alpha y}\mu e^{-\mu y}dy = \mu\int_0^\infty e^{-(\mu - t\alpha)y}dy = \frac{\mu}{\mu - t\alpha} = \frac{(\mu/\alpha)}{(\mu/\alpha) - t}. \tag{4.6}$$

Since the moment generation function of exponential distribution with parameter μ is known as $\frac{\mu}{\mu - t}$ and on the other hand the moment generating function uniquely determines the distribution, it is concluded that αy is exponentially distributed with rate μ/α,

$$\alpha y \sim Exponential(\mu/\alpha). \tag{4.7}$$

Knowing the distribution of αy, distribution of daily demand and properties of compound distributions, distribution of demand can be found. According to compound distribution properties, compounding a Poisson distribution with rate parameter distributed according to a gamma distribution yields a negative binomial distribution. Since exponential distribution is a special case of gamma distribution, demand during shortage follows negative binomial distribution with $r = 1$ and $p = 1/(1 + \mu/\alpha)$,

$$d_{shortage} \sim NegativeBinomial(1, \frac{1}{1 + \mu/\alpha}). \tag{4.8}$$

Knowing the distribution of demand during the shortage, probability of each demand scenario $p(\omega)$ can be calculated. Therefore, equation (4.4) is ready for optimization after plugging $p(\omega)$ and other parameters given in Table 4.1. The resulting formulation is linear and General Algebraic Modeling System (GAMS) is used to optimize the problem. Since the number of scenarios is high, an extension of Monte Carlo approach is used to solve the problem. All possible demand scenarios are categorized in 10 groups. The first group is starting from demand zero to $10th$ percentile of demand. The last group is from $90th$ percentile to $99.99th$ percentile of demand. The expected value of each group is defined as representative of the group. Since negative binomial distribution is not limited, the maximum possible demand is assumed to be

99.99% percentile of the binomial distribution.

The optimization model minimizes the total cost of the system. Therefore, when shortage cost and shipping cost are identical for hospitals receiving the items, no hospital has priority over others in receiving as far as it is facing shortage. Therefore, one shortcoming of the results of the optimization model is that the distribution of the items among hospitals may not be balanced. Considering the equal impact of the shortage at all hospitals, the shortage cost is identical for all hospitals. Therefore unbalanced results may happen in situation when shipping costs are identical. To resolve this problem, we developed a heuristic algorithm for three hospitals to balance the items received by each hospital proportional to their initial inventory level before shortage period. This algorithm can easily be extended for more than three hospitals. In this algorithm, algorithm 2, the results of optimization modeling for each scenario are balanced so identical hospitals receive equal amount of drugs while they are in shortage. This algorithm should be run for each demand scenario to find the balanced results.

Algorithm 2 Heuristic Algorithm for Balancing Results in Identical Hospitals
INPUT: d_1, d_2, d_3, y_1, y_2, y_3, x_{12}, x_{13}, x_{21}, x_{23}, x_{31}, x_{32}
OUTPUT: x'_{12}, x'_{13}, x'_{21}, x'_{23}, x'_{31}, x'_{32}

$j \leftarrow$ Index of the hospital that shares the maximum amount
$k \leftarrow$ Index of the hospital that shares the second maximum amount
$t \leftarrow$ Index of the hospital that shares the minimum amount
{**Case 1: No sharing**}
if $x_{jk} + x_{jt} = 0$ **then**
  Break
  {**No Sharing exist**}
end if
{**Case 2: One hospital shares**}
if $x_{kj} + x_{kt} = 0$ **then**
  $x'_{jk} \leftarrow min\{(d_k - y_k), (\frac{x_{jk} + x_{jt}}{y_k + y_t} y_k)\}$
  $x'_{jt} \leftarrow min\{(d_t - y_t), \max\{(\frac{x_{jk} + x_{jt}}{y_k + y_t} y_t), (x_{jk} + xjt - x'jk)\}\}$
  $x'_{jk} \leftarrow min\{x'_{jk}, (x_{jk} + x_{jt} - x'jt)\}$
end if
{**Case 3: Two hospitals share**}
if $x_{kj} + x_{kt} > 0$ **then**
  $x'_{jt} \leftarrow min\{(x_{jk} + x_{jt}), (\frac{x_{jt} + x_{kt}}{y_j + y_k} y_j)\}$
  $x'_{kt} \leftarrow min\{(x_{kj} + x_{kt}), \max\{(\frac{x_{jt} + x_{kt}}{y_j + y_k} y_k), (d_t - y_t - x'_{jt})\}\}$
  $x'_{jk} \leftarrow min\{x'_{jt}, (d_t - y_t - x'_{kt})\}$
end if

4.4 Computational Results and Sensitivity Analysis

To analyze the interaction among hospitals during the shortage, three main scenarios for three hospitals are assumed. First all hospitals have identical demands and warehouse capacity. In the second scenario, the first hospital's demand rate is twice, that of other hospitals while they have equal warehouse capacity. The third scenario assumes equal demand rate for all hospitals while the warehouse capacity of the first hospital is twice as much as the others. Costs are identical in all these hospitals. The cost and capacity parameters used for analysis are related to a drug with daily demand rate of 4 that occupies the 21% of the warehouse space of the hospital introduced in section 3.4.4.

The result of the first scenario is illustrated in Fig. 4.1. Demand in hospital 1 is shown in the x axis. When demand of hospital 1 is less than its available inventory level, it shares the extra inventory with hospital 2 and 3 equally. Because of the identical properties of hospital 2 and 3, the number of items that each of them share with hospital 1 is equal and also they share an equal amount with each other. Since both hospital 2 and 3 receive items from hospital 1 when demand of hospital 1 is low, they share more items with hospital 1 than with each other when demand of hospital 1 is high. The same figure can be drawn for hospital 2 and 3. Since the characteristics of these hospitals are identical, the figure is the same. Therefore, similar analysis will arise.

The results of the second scenario are illustrated in Fig. 4.2 and Fig. 4.3. In Fig. 4.2 demand in hospital 1 is shown in the x axis. Since hospital 2 and 3 are identical, the amount that hospital 1 shares with them is equal. Compared to scenario 1, Fig. 4.1, the first hospital shares under less demand scenarios because it faces more demand while its warehouse capacity is the same as the first scenario. Hospital 2 and 3 are identical therefore they share an equal amount with hospital 1. This amount

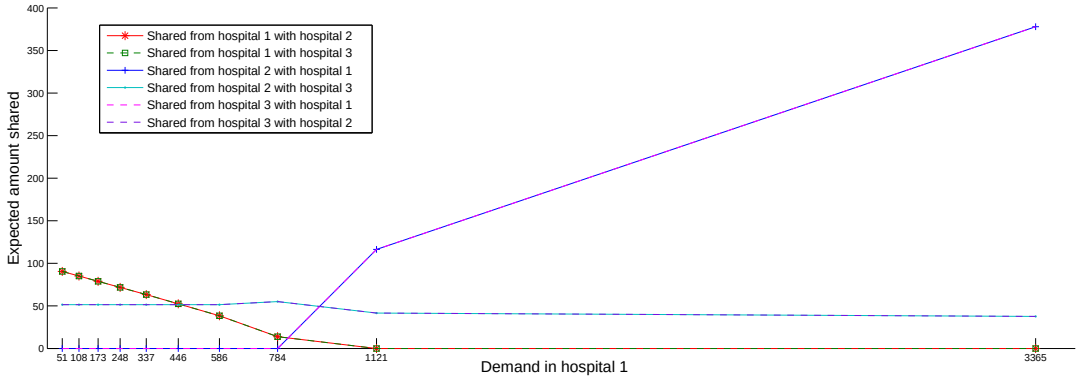

Figure 4.1: Sensitivity Analysis of expected number of sharing among hospitals relative to demand in hospital 1 (First scenario)

is more than what they share with each other because the demand in hospital 1 is more and balance in sharing needs to be considered. It is easy to see that they will share more with each other when hospital 1 is not facing shortage. Fig. 4.3 shows

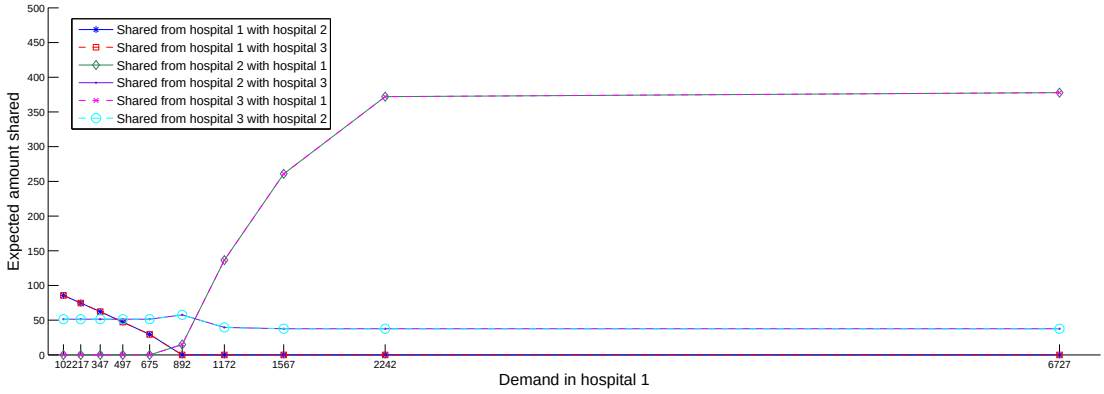

Figure 4.2: Sensitivity Analysis of expected number of sharing among hospitals relative to demand scenarios in hospital 1 (Second scenario)

the sharing among different hospitals relative to the demand scenario in hospital 2. When demand in hospital 2 is low it shares more items with hospital 1 than hospital 3 because hospital 1 has a higher demand rate and it will face shortages more. It is easy to comprehend that hospital 2 will not share when its demand is more than its available inventory level. When demand of hospital 2 faces shortages, hospital 3

shares more items with hospital 2 than it shares with hospital 1 because it shares some items with hospital 1 while hospital 2 is not in shortage. Hospital 1 has similar interaction. It shares more items with hospital 2 than it shares with hospital 3. Fig. 4.3 can be drawn based on demand scenarios in hospital 3 but since hospital 2 and 3 are identical these graphs will be same. The results of the third scenario

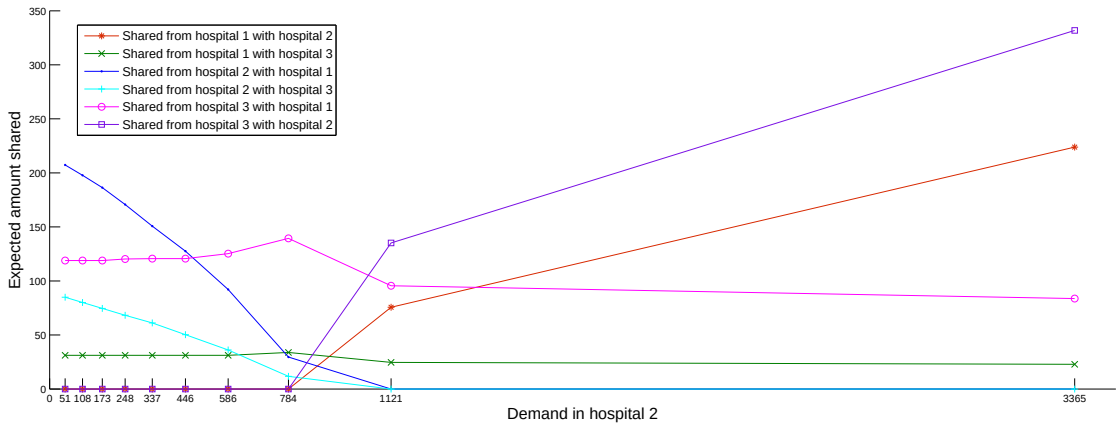

Figure 4.3: Sensitivity Analysis of expected number of sharing among hospitals relative to demand scenarios in hospital 2 (Second scenario)

are presented in Fig. 4.4 and Fig. 4.5. In this scenario demand rates are identical while the capacity of hospital 1 is twice of hospital 2 and 3. Because of the higher warehouse capacity, when demand of hospital 1 is low the maximum items that it shares is more than in the case that the capacities are identical. It will share same amount with hospital 2 and 3 because they are identical. The amount that hospital 2 and 3 are sharing with hospital 1 is more than amount they share with each other because they receive items when its demand is low and the balance for sharing needs to be considered. Fig. 4.5 illustrates the sharing interactions among hospitals based on the demand scenarios for hospital 2. When demand of hospital 2 is low, it shares more items with hospital 3 than hospital 1 because hospital 1 has more capacity and will face shortages less. Comparing Fig. 4.5 with Fig. 4.3, the amount that hospital 2 shares with hospital 1 is more in the second scenario. It happens because when

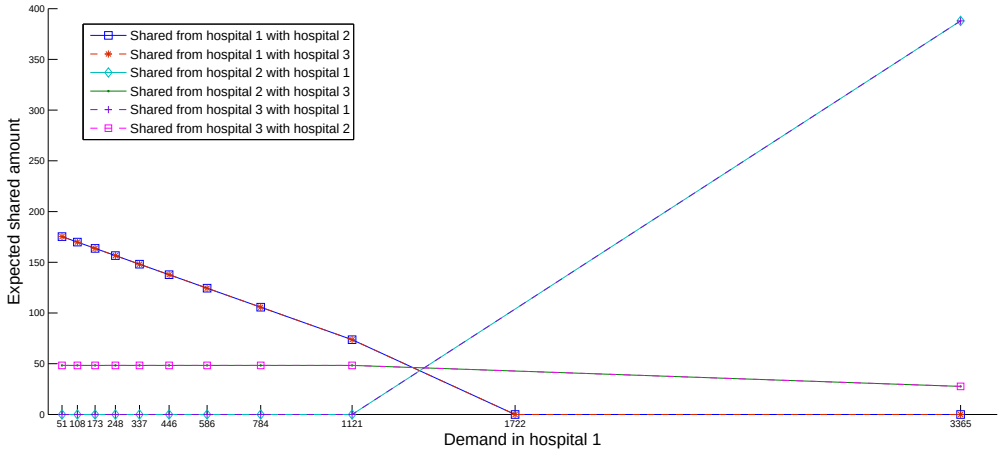

Figure 4.4: Sensitivity Analysis of expected number of sharing among hospitals relative to demand scenarios in hospital 1 (Third scenario)

demand rate of hospital 1 is twice it will face more shortage and it receives more but in third scenario it faces less shortages. When demand is high in hospital 2, hospital 1 shares more items with hospital 2 than hospital 3 because it receives item when demand in hospital 2 is low. The amount hospital 3 shares with hospital 2 is more than what it shares with hospital 1 because hospital 1 faces less shortages. This figure can be drawn based on demand scenarios in hospital 3 but hospital 2 and hospital 3 are identical and the result will be same as current figure.

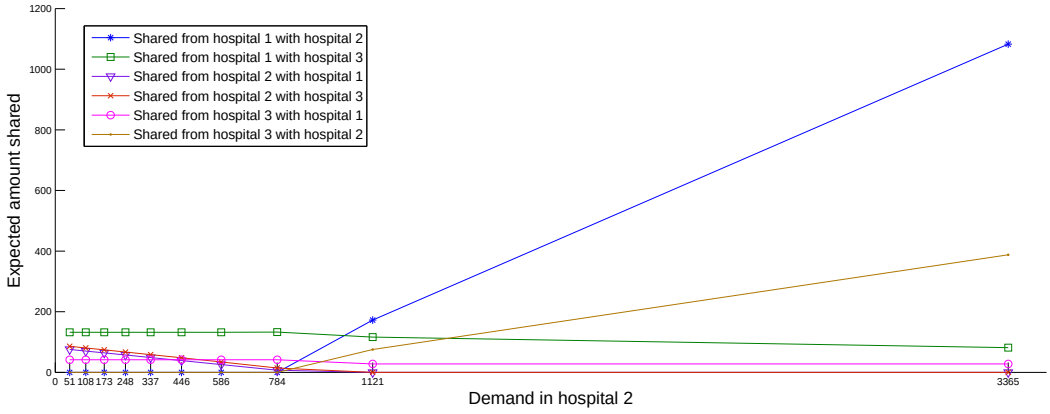

Figure 4.5: Sensitivity Analysis of expected number of sharing among hospitals relative to demand scenarios in hospital 2 (Third scenario)

As it is discussed in section 4.1, collaborators are willing to stay in collaboration if their benefits are higher in collaboration. Considering the affect of shortages in service level of the hospitals their ultimate goal is minimizing their shortages when their demand is more than their inventory level and minimizing their holding cost when their demand is less than their inventory level. Table 4.2 is showing the expected number of shortage in each hospital j, z_j, and expected number of extra items in warehouse for all three scenarios. To calculate expected number of shortages equation (4.9) is used,

$$E(z_j) = \sum_{\omega=1}^{\Omega} z_j^{\omega} p_{\omega} \approx z_j^{\omega} p_{\omega} \qquad \omega = 1, ..., 10. \tag{4.9}$$

Scenario	**Hospital**	**Collaboration status**	**Expected number of shortages**	**Expected number of left overs in warehouse**
1	**1,2,3**	Collaboration	178	317
		No Collaboration	276	415
2	**1**	Collaboration	597	187
		No Collaboration	830	247
	2,3	Collaboration	200	253
		No Collaboration	276	415
3	**1**	Collaboration	87	312
		No Collaboration	164	415
	2,3	Collaboration	105	330
		No Collaboration	276	415

Table 4.2: Expected number of shortages and extra items in warehouse for each hospital under 3 different scenarios

According to Table 4.2, the maximum reduction in number of shortage for this drug using collaboration synergy happens when a hospital is collaborating with another hospital that has same capacity but half demand rate. Minimum reduction in number of shortages using collaboration synergy happens when a hospital collaborates with a smaller hospital or a hospital with same size but twice demand. Maximum reduction in left overs happens when hospital shares with another hospital with twice demand.

4.5 Concluding Remarks

This chapter provides a hospital with a structure for its inventory sharing based on information that it has from other collaborators. The game theory model results in a collaboration which is beneficial for each hospital. It minimizes the shortage cost in each hospital while it minimizes the holding cost of the items. To balance the result of the game theory model in such a way that identical hospitals receive equal amount of item, a heuristic algorithm is developed which using the result of game theory model as input will give a balanced structure for sharing. The model is verified using sensitivity analysis on shortage rate and as it is expected when shortage rate increases, hospitals are willing to share more. An immediate extension for this work is developing a structure for scheduling the sharings during the shortage period. In current model it is assumed that when hospitals enter the shortage period after few days they have an estimation about their demand during shortage and can start sharing their excess inventory. While the current model defines the amount of sharing among hospitals, it does not give a schedule for doing the sharing during the shortage period. In current study hospitals are purchasing just from a single hospital while in reality when hospitals are not able to receive their demand through their common supplier, they have purchase limited number of drugs with higher price from secondary vendors. Therefore a possible directions for future research is assuming more than one supplier for the hospitals with different ordering costs.

Chapter 5

Summary and Future Study

This dissertation presents two major problems in healthcare area: (i) diabetic foot ulcer prevention, and (ii) mitigating the impact of national pharmaceutical shortages. In this chapter, summary of dissertation and future extensions are presented.

5.1 Analysis for Diabetic Foot Ulcers (DFU) Primary and Secondary Prevention Strategies

As mentioned in Chapter 2, the goal of this study is answering two main questions. First, finding the affect of timely treatment in different groups of patients. Second analyzing the affect of primary preventive strategies and the threshold value of the primary preventive strategies for each group of patients. To answer these questions a decision support system is designed using a cost-effectiveness analysis along with sensitivity analysis.

All patients are divided into three groups based on two critical risk factors in diabetic patients: Neuropathy and Peripheral arterial disease. Based on the group that the patient belongs to, the strategy for providing timely treatment and primary prevention varies. According to the results, around 10% of PACT 1 should receive timely treatment to minimize the expected total cost of the system. For this group of patients, 10% is the break even point for expected amputation cost resulted from getting treatment and expected infection cost resulting from not getting treatment. All PACT 2 patients need to receive timely treatment to minimize the expected total cost of the system and expected number of amputations. Ten percent of PACT 3 patients should receive timely treatment. This point is the break even point for

expected revascularization cost for treated patients and expected amputation cost for non treated patients. According to sensitivity analysis for primary prevention strategies, minimum cost per prevented ulcer happens when around 90% of patients in all groups receive primary prevention. Applying these strategies will result in higher cost while it will decrease number of developed ulcers. This analysis, section 2.4.2, can also help healthcare decision makers to find their optimal prevention strategy by defining a value for each prevented ulcer. Possible extensions of current model can be done by adding more risk factors and increase number of possible groups that each patients can belong to. Although, finding the incident rates for the other group of patients based on available literature is very challenging. Another interesting setting is adding the different states of limb loss and their associated costs to the model to have a more detailed analysis on patients that go though amputation.

5.2 Pharmaceutical Supply Chain Analytics

As discussed in Chapter 1, two practical approaches to help solving national drug shortages are: (i) single hospital critical inventory planning and (ii) collaborative hospital inventory sharing. In Section 5.2.1, the conclusion and future extensions of the first study will be discussed. Next, the conclusion and future extensions of Game Theory approach for inventory sharing will be presented.

5.2.1 Individual Pharmaceutical Inventory Control Problem under Uncertainty

Conventional inventory models consider the tradeoff between different costs of an item and achieving an optimal solution even in the case of unlimited capacity. What makes pharmaceutical supply chains unique is a set of attributes such as zero lead time, zero fixed-cost ordering, supply disruption, item substitution, and importance

of service levels, implying a high warehouse utilization independent from the size. Therefore, we seek to find the balance point between items, considering the space occupied by an item, disruption rates, expected duration of a disruption (i.e., recovery rate), demand rate, as well as substitute item's disruption rate and duration. To achieve this objective, Chapter 3 introduced two stochastic models using continuous time Markov chain method. First model utilized drug substitution and minimized shortages but disregarded holding and substitution costs. Its objective was finding the optimal reorder point level for different drugs considering a predefined warehouse capacity. This model was solved by General Algebraic Modeling System (GAMS) with CONOPT solver. Using simulation, our results were compared with current inventory strategy as well as an (s, S) policy from the literature (Arreola-Risa and DeCroix, 1998). It should be noted that the setting introduced by Arreola-Risa and DeCroix (1998) was not a perfect fit for the pharmaceutical problem, thus we modified the way our input parameters were fed to the algorithm for better solution quality. Proposed strategy showed a significant improvement in comparison with other two strategies. Second model, utilized drug substitution and minimized total costs of the system while had both safety stock level and order quantity level as model variables. The objective of this model was finding optimal reorder point level as well as order quantity for each drug. Since exact procedures for solving current model did not have a good time performance, development of an approximation or heuristic method was necessary. A two phase heuristic algorithm was developed for the problem. The results showed that the proposed scheme is better compared to the current policies in all aspects of the inventory in a healthcare facility except for the holding cost, which is expected due to the currently low utilization of space.

One of the major problems in pharmacies is inventory inaccuracies. Inventory inaccuracy happens when real number of drugs in inventory is different from the value entered for inventory management purposes. Considering inventory inaccuracy

in model adds another stochasticity and illustrates the real world problem in a hospital's pharmacy. Substitute items often cost more than mainstream drugs and may go short, however no model in the literature, to the best of our knowledge, utilizes that information. We assume that some of the drugs have substitutes and if they are available substitution can be performed with some cost. An interesting immediate extension of the model would be considering items with more than one substitute. Furthermore, there is a *quality of service* aspect related to substitutes. A substitute may not be as effective as a mainstream drug for all patients. Some substitutes may not be preferred agents although they might be less expensive such as sodium bicarbonate (substituting tromethamine) or capecitabine (substituting fluorouracil). A multi-criteria framework can consider the total cost similar to a conventional inventory model on one dimension and the quality of service that assesses the impacts of shortage and substitution on another. Rather than one optimal solution, a set of solutions on the efficient frontier can be further evaluated under different conditions.

5.2.2 Inventory Sharing

Inventory sharing as one of the actions for facing shortages, is studied using a game theory structure in this dissertation. Coordinated ordering allows hospitals to incur reduced shortage and inventory costs. We developed a game-theoretic model using an exciting model in literature. The optimization problem was a two stage stochastic programming which was solved using the deterministic equivalent of the model. It was a large linear optimization problem that for simplifying it all possible demand scenarios are categorized into 10 groups. First group was all demand between zero and the $10th$ percentile of the distribution of demand during shortage. The last group included all demands between $9th$ percentile to $99.99th$ percentile of the distribution of demand during shortage. Results gave insight to the hospitals that are willing to collaborate in defining a strategy for amount that they share and the

sharing interactions based on other hospitals information. In this study hospitals were purchasing from a single hospital while in reality when hospitals are not able to receive their demand through their usual supplier, they have some back up providers and they can purchase limited number of drugs with higher price from them. Therefore a possible directions for future research would be assuming more than one supplier for the hospitals with different ordering costs. Another promising direction of future research is investigating a structure for scheduling the shadings during the shortage period. In current model it is assumed that when hospitals enter the shortage period after few days they have an estimation about their demand during shortage and can start sharing their excess inventory. While current model defines the amount of sharing among hospitals but it does not give a schedule on sharing during the shortage period.

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