SUPPLY CHAIN MANAGEMENT OF PERISHABLE PRODUCTS WITH APPLICATIONS TO HEALTHCARE

A Dissertation Presented

by

AMIRHOSSEIN MASOUMI

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2013

Isenberg School of Management

SUPPLY CHAIN MANAGEMENT OF PERISHABLE PRODUCTS WITH APPLICATIONS TO HEALTHCARE

A Dissertation Presented

by

AMIRHOSSEIN MASOUMI

Approved as to style and content by:

Anna Nagurney, Chair

Hari Balasubramanian, Member

June Qiong Dong, Member

Senay Solak, Member

D. A. Butterfield, Ph.D. Program Director
Isenberg School of Management

To my family.

ACKNOWLEDGMENTS

I would like to acknowledge many people for helping me during my doctoral studies at the Isenberg School of Management and the Industrial Engineering Department.

First and foremost, I should thank my esteemed advisor, John F. Smith Memorial Professor Anna Nagurney, for providing me with the opportunity to obtain my PhD degree in Management, and for continuously caring about my studies. Indeed I learned a lot from Professor Nagurney's leadership, her inspiring passion for research, and her supporting of her current and former students.

I am very grateful for having had an outstanding dissertation committee, and would like to thank my committee members Professors June Dong, Senay Solak, and Hari Balasubramanian for their thoughtful insights on my dissertation, and for their exceptional support during my job searching process.

I am also very thankful to Professors Iqbal Agha, Anthony Butterfield, Ahmed Ghoniem, Donald Fisher, and James Smith for their advice and support throughout my years at UMass Amherst. I extend my thanks to Audrey Kieras, Sarah Malek, Mary Parker, Ellen Pekar, Lynda Vassallo, Jacqui Urban, Lou Wigdor, Cerrianne Fisher, Diane Kelley, and Dorothy Adams for their administrative support.

My special thanks go to my colleagues at the Virtual Center for Supernetworks in past and present: Professors Ladimer Nagurney, Patrick Qiang, Jose Cruz, Leo Liu, Dmytro Matsypura, Tina Wakolbinger, Trisha Woolley-Anderson, and to Michelle Li, Sara Saberi, and Shivani Shukla. My very special thanks go to Dr. Min Yu for four years of collaboration throughout the doctoral program.

Last but not least, I would like to thank my wife, Azita, for always encouraging me in pursuit of my dreams.

ABSTRACT

SUPPLY CHAIN MANAGEMENT OF PERISHABLE PRODUCTS WITH APPLICATIONS TO HEALTHCARE

MAY 2013

AMIRHOSSEIN MASOUMI

B.Sc., ISFAHAN UNIVERSITY OF TECHNOLOGY

M.Sc., AZAD UNIVERSITY OF TEHRAN – SCIENCE & RESEARCH CAMPUS

Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Anna Nagurney

Supply chains for time-sensitive products, and, in particular, for perishable products, pose specific and unique challenges. By definition, a perishable product has a limited lifetime during which it can be used, after which it should be discarded (Federgruen, Prastacos, and Zipkin (1986)).

In this dissertation, I contribute to the analysis, design, and management of supply chain networks for perishable products with applications to healthcare.

Specifically, I construct generalized network frameworks to capture perishable product supply chains in healthcare operating under either centralized or decentralized decision-making behavior. The dissertation is motivated by applications ranging

from blood supply chains to pharmaceuticals, such as vaccines and medicines. The novelty of the modeling and computational framework includes the use of arc multipliers to capture the perishability of the healthcare product(s), along with waste management costs, and risk.

The first part of the dissertation consists of a literature review of perishable product supply chains with a focus on healthcare along with an overview of the relevant methodologies.

The second part of the dissertation formulates supply chains in healthcare operating under centralized decision-making behavior. In this part, I focus on both the operations management of and the sustainable design of blood supply chains and construct models for regionalized blood banking systems as belonging to the Red Cross.

The third part of the dissertation considers competitive behavior, with a focus on the pharmaceutical industry. I construct an oligopoly supply chain network model, with differentiated brands to capture the competition among producers of substitutable drugs using game theory and variational inequality theory. Furthermore, using a case study based on real-world scenarios of a highly popular cholesterol-reducing branded drug, the impact of patent rights expiration of that brand is explored which coincides the time when its equivalent generic emerges into the markets. The calculated results are then compared to the observations from the real-word problem. Finally, the projected dynamical system formulation of the pharmaceutical network oligopoly model is derived.

This dissertation is based on the following papers: Nagurney, Masoumi, and Yu (2012), Nagurney and Masoumi (2012), and Masoumi, Yu, and Nagurney (2012) as well as additional results and conclusions.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure **Page**

CHAPTER 1

INTRODUCTION AND RESEARCH MOTIVATION

Supply chains, by definition, are the essential infrastructure for the production, distribution, and consumption of goods as well as services in today's globalized network economy, and, in their most basic realization, consist of manufacturers and suppliers, distributors, retailers, and consumers at the demand markets (Nagurney (2006)).

Accordingly, the phrase "supply chain management" (SCM) is defined as the management of a network of interconnected businesses involved in the ultimate provision of product and service packages required by end customers (Harland (1996) and Christopher (2005)). Although this term has been used for different purposes since it was originated by Oliver and Webber (1982), SCM, in general, spans all movement and storage of raw materials, work-in-process inventory, and finished goods from the origin to the destination points. Consequently, various issues of producers and service providers including but not limited to network configuration, information flow, inventory management and operations management are all discussed in supply chain management. Furthermore, the management of different types of goods and services ranging from energy to healthcare products is being undertaken by supply chain management specialists.

Today's supply chains, in contrast to their earlier versions, are more complex, and, as a result, are widely exposed to ever-increasing challenges. Consumers' demand for new products, the globally critical economic situation as well as the uprising environmental concerns require that companies, as well as organizations, be more innovative

while also becoming more cost-effective in the procurement, production, and distribution of their products and services. Nevertheless, despite numerous significant achievements, the discipline of supply chain management is still incapable of satisfactorily addressing many practical, real-world challenges (Georgiadis, Vlachos, and Iakovou (2005)).

When it comes to the supply chains of products with a limited lifespan, these challenges become of further concern for the managers and decision-makers. By definition, a "perishable product" has a limited lifetime during which it can be used, after which it should be discarded (Federgruen, Prastacos, and Zipkin (1986)). Examples of perishable goods include dairy products, baked goods, fruits and vegetables, medicines and vaccines, cut flowers, etc. (Or and Pierskalla (1979), Prastacos (1984), Zanoni and Zavanella (2007), Osvald and Stirn (2008), Ahumada and Villalobos (2009), and Nahmias (2011)). Supply chain management of perishable products typically poses unique challenges at the strategic, tactical, and operational levels of an organization's decision-making hierarchy due to the following reasons:

- *Transportation and storage*: The majority of perishable products demand careful handling, special transportation equipment, and cold storage facilities to ensure that the quality is preserved until the expiration date.

- *Inventory management*: At the demand points as well as the other facilities of the supply chain, inventory tracking and replenishment techniques need to be utilized to minimize the outdating/deterioration of such products.

- *Safety*: Perishable products are very often prone to not only lose their freshness but also to become hazardous if not distributed/used within their lifetimes.

- *Incurred waste discarding cost*: Discarding the waste/perished goods imposes an additional cost to the firms.

- *Environmental impact*: The produced waste - which can be potentially hazardous - can pollute the soil, the air, and the water each of which, in turn, can lead to diseases.

The study of perishable products operations management is often linked to the study of healthcare supply chains. In fact, specific healthcare products have always been considered distinct cases in the study of perishable goods supply chains. This is mainly due to the significance of the availability and timeliness of medical care product and service provision. This, coupled with the rising concerns on the reliability and safety of health-related products, has further complicated the management of such supply chain networks.

In this dissertation, I contribute to the analysis, design, and management of supply chain networks for perishable products with applications to healthcare.

Specifically, I construct generalized network frameworks to model perishable product supply chains in healthcare operating under either centralized or decentralized decision-making behavior. The dissertation is motivated by applications ranging from blood supply chains to pharmaceuticals, such as vaccines and medicines. The novelty of the modeling and computational framework includes the use of arc multipliers to capture the perishability of the healthcare product(s), along with waste management costs, and risk.

The first part of the dissertation, Chapters 1 and 2, consists of a literature review of perishable product supply chains with a focus on healthcare along with an overview of the relevant methodologies, including network theory, optimization theory, variational inequality theory, multicriteria decision making, and projected dynamical systems.

The second part of the dissertation, Chapters 3 and 4, formulates supply chains in healthcare operating under centralized decision-making behavior. In this part, I focus on both the operations management of and the sustainable design of blood

supply chains and construct models for a regionalized blood banking system of the Red Cross.

The third and final part of the dissertation consists of Chapter 5 and 6. Chapter 5 considers competitive behavior, with a focus on the pharmaceutical industry. More specifically, I construct an oligopoly supply chain network model, with differentiated brands to capture the competition among producers of substitutable drugs using game theory, variational inequality theory, and projected dynamical systems theory. Chapter 6 summarizes the dissertation and provides suggestions for future research.

This chapter is organized as follows: I first provide an overview and research motivation in Section 1.1. In Section 1.2, I present the literature review for each of the relevant applications, including perishable products supply chains, healthcare supply chain systems, blood banking systems, and pharmaceutical supply chains. Finally, in Section 1.3, I provide a more detailed overview of the dissertation.

1.1. Research Motivation

Natural disasters are growing all over the world. According to the National Oceanic and Atmospheric Administration (NOAA), in the US alone, the average number of disasters per year that exceeded a cost of 1 billion dollars in damages increased from 3.6 in the 2001-2005 period to 5.8 in 2006-2010. During the first six months of 2011, eight extreme weather events set a new record for such events in one year. Scientists have warned that we should expect cases of extreme events even more in the future (Sheppard (2011)).

My research is motivated by two healthcare supply chains – human blood and pharmaceutical ones. These are relevant in times of crisis and in more normal times. Below I overview the previous background and the motivation for research on these two healthcare supply chains.

The need for blood - as the need for other healthcare products - is, however, not limited to times of crisis. Under normal circumstances, every two seconds someone in the US requires a blood transfusion. According to the American Red Cross, over 39,000 donations are needed everyday in the United States, alone, and the blood supply is frequently reported to be just 2 days away from running out. Of 1,700 hospitals participating in a survey in 2007, a total of 492 reported cancellations of elective surgeries on one or more days due to blood shortages. Shockingly, hospitals with as many days of surgical delays as 50 or even 120 have also been observed (Whitaker et al. (2007)).

The major consumers of blood products are hospitals where blood is transfused to trauma victims as well as the patients dealing with surgeries, organ transplants, leukemia, and other diseases. The demand for blood products always exists yet can never be known in advance with certainty. Thus, having a blood banking system with sufficient stocks of available fresh blood is a key component of every healthcare system all across the globe.

Consequently, human blood banking systems are among the most dominant perishable healthcare supply chains to have been researched. Nahmias (1982) claimed that: "The interest among researchers in perishable inventory problems has been sparked primarily by problems of blood bank management. Some of the possible reasons for this interest might be that blood bank research has been supported by public funds." Whether or not Nahmias' statement is still valid - considering all the recent concerns about the safety of perishable products - blood bank management from a supply chain network perspective merits a fresh and updated approach. This topic is especially timely today, since - as mentioned earlier - the number of disasters and the number of people affected by disasters has been growing over the past decade and blood is certainly a life-saving product (cf. Nagurney and Qiang (2009)).

Note that, according to the World Health Organization (WHO), numerous countries have established completely voluntary (unpaid) blood donation systems, and WHO's target is to have this goal achieved for every country in the world by 2020 (The Pakistan Observer (2011)). Nevertheless, due to the scarcity of human blood, and the ever growing cost of procurement of blood products, the blood banking systems must be cost-efficient by minimizing the total number of outdated units of this valuable yet highly perishable product.

Even though the 2007 National Blood Collection and Utilization Survey suggests that the hospitals and the blood centers continue to improve the efficiencies in the delivery of blood products, in 2006, 1,276,000 units, i.e., more than 8% of the total 15,688,000 units of the US national blood supply were outdated by blood centers and hospitals (Whitaker et al. (2007)). Hospitals were responsible for approximately 90% of these outdates, where this volume of waste imposes discarding costs to the already financially-stressed hospitals (Chen (2010)).

Considering also the ever-increasing hospital cost of a unit of red blood cells with a 6.4% increase from 2005 to 2007 further highlights the criticality of this perishable, life-saving product. In the US, this criticality has become more of an issue in the Northeastern and Southwestern states since this cost is meaningfully higher compared to that of the Southeastern and Central states (Whitaker et al. 2007).

Apart from the concern about the operational costs, environmental safety is another significant challenge that the blood banking systems are dealing with. Disposal of the produced waste throughout the blood banking supply chain not only incurs additional costs to the system, but also contributes to the healthcare facilities' being second only to the food industry in the US in producing waste, generating more than 6,600 tons per day, and more than 4 billion pounds annually (Fox News (2011)).

The waste produced throughout the blood banking supply network, either as a result of the expiration of the blood products' lifetime, or as the potential outcome of

of the lab tests, is also a threat to the environment. By definition, "medical waste", also known as clinical waste, refers to the waste products that can not be considered as general waste, and that is produced, typically, at healthcare premises, including hospitals, clinics, and labs. Due to the potentially hazardous nature of medical waste, both the American Dental Association (ADA) and the Centers for Disease Control (CDC) recommend that medical waste be removed in accordance with regulations (Pasupathi et al. (2011)).

Consequently, poor management of such waste may lead to the contamination of water, the soil, and the atmosphere. While many hospitals choose to have their waste burned so as to avoid polluting the soil through landfills, the incinerators themselves are one of the nation's leading sources of toxic pollutants such as dioxins and mercury (Giusti (2009) and Association of Bay Area Governments (2003)). Thus, minimizing the amount of medical waste throughout healthcare supply chains will lead to a cleaner environment, which may, in turn, also reduce illnesses and death.

On the other hand, from a product safety perspective, there exists a definable risk associated with the transfusion of blood and blood products including infections, immune reactions, and human and testing errors (Slonim, Bish, and Xie (2011)). In the US, federal law mandates that every single unit of donated blood be tested before being transfused regardless of the age, the gender, and the number of times a donor has donated blood in the past. At the same time, blood testing is the costliest activity in the entire blood banking supply chain network.

Interestingly, the Red Cross has shuttered several of its blood centers as well as testing labs across the country since 2008 as a part of a five–year plan to offset the organization's $209 million annual operating deficit (Hunt (2012)). Like many other nonprofit organizations, the Red Cross is facing tough economic decisions. All blood services organizations in the US are nonprofit, and the Red Cross's being in charge of almost half of blood collections nationwide further highlights the criticality

of this life-saving product (Rios (2010) and Walker (2010)). Although the closure of these facilities has reduced the overall costs of the organization, it has increased the transportation costs of blood products between the remaining facilities.

Another key perishable health-related product supply chain, and a fundamental element of healthcare systems, is that of pharmaceutical firms. Pharmaceutical, that is, medicinal drug, manufacturing is an immense global industry. In 2003, worldwide pharmaceutical industry sales were at $491.8 billion, an increase in sales volume of 9% over the preceding year with the US being the largest national market, accounting for 44% of global industry sales (cf. The Health Strategies Consultancy LLC (2005)). In 2011, the global pharmaceutical industry was expected to record growth of 5-7% on sales of approximately $880 billion (Zacks Equity Research (2011)).

Although pharmaceutical supply chains have begun to be coupled with sophisticated technologies in order to improve both the quantity and the quality of their associated products (Yost (2005) and Breen and Crawford (2005)), despite all the advances in manufacturing, storage, and distribution methods, certain pharmaceutical drug companies are far from effectively satisfying market demands on a consistent basis. It has been argued that pharmaceutical drug supply chains are in urgent need of efficient optimization techniques in order to reduce costs, and to increase productivity and responsiveness (Shah (2004) and Papageorgiou (2009)).

Similar to blood banking systems, product perishability is also an issue in pharmaceutical/drug supply chains. In a 2003 survey, the estimated incurred cost due to the expiration of branded products in supermarkets and drug stores was over 500 million dollars (Grocery Manufacturers of America (2004)). In 2007, in a warehouse belonging to the Health Department of Chicago, over one million dollars in drugs, vaccines, and other medical supplies were found spoiled, stolen, or unaccounted for (Mihalopoulos (2009)). In 2009, CVS pharmacies in California, as a result of a settlement of a lawsuit filed against the company, had to offer promotional coupons

to customers who had identified expired drugs, including expired baby formula and children's medicines, in more than 42 percent of the stores surveyed the year before (WPRI (2009) and Business Wire (2009)). Other instances of medications sold more than a year past their expiration dates have occurred in other pharmacies across the US (WABC (2008)). According to the Harvard Medical School (2003), since a law was passed in the US in 1979, drug manufacturers are required to stamp an expiration date on their products. This is the date at which the manufacturer can still guarantee the full, that is, 100%, potency and safety of the drug, assuming, of course, that proper storage procedures have been followed. For example, certain medications, including insulin, must be stored under appropriate environmental conditions, and exposure to water, heat, humidity or other factors can adversely affect how certain drugs perform in the human body. Nevertheless, the majority of over-the-counter medications such as headache relievers merely become less potent - not dangerous - over time.

Ironically, whereas some drugs may be unsold and unused and/or past their expiration dates, the number of drugs that were reported in short supply in the US in the first half of 2011 rose to 211 – close to an all-time record – with only 58 in short supply in 2004 (Emanuel (2011)). According to the Food and Drug Administration (FDA), hospitals have reported shortages of drugs used in a wide range of applications, ranging from cancer treatment to surgery, anesthesia, and intravenous feedings. The consequences of such shortages include the postponement of surgeries and treatments, and may also result in the use of less effective or costlier substitutes. According to the American Hospital Association, all US hospitals have experienced drug shortages, and 82% have reported delayed care for their patients as a consequence (Szabo (2011)).

While the real causes of such shortages are complex, most cases appear to be related to manufacturers' decisions to cease production in the presence of financial challenges. It is interesting to note that, among curative cancer drugs, only the

older generic, yet, less expensive, ones, have experienced shortages. As noted by Shah (2004), pharmaceutical companies secure notable returns solely in the early lifetime of a successful drug, before competition takes place. This competition-free time-span, however, has been observed to be shortening, from 5 years to only 1-2 years. Hence, the low profit margins associated with such drugs may be forcing pharmaceutical companies to make a difficult decision: whether to lose money by continuing to produce a lifesaving product or to switch to a more profitable drug. Unfortunately, the FDA cannot force companies to continue to produce low-profit medicines even if millions of lives rely on them (Emanuel (2011) and Szabo (2011)). On the other hand, where competition has been lacking, shortages of some other lifesaving drugs have resulted in huge spikes in prices, ranging from a 100% to a 4,500% increase with an average of 650% (Schneider (2011)).

In addition to increasing generic competition, the lower reimbursements by government health programs have worsened the situation. For example, Merck & Co., Inc., the multinational pharmaceutical giant, in 2011, announced more than 13,000 layoffs, to be completed by 2015, so as to offset costs by lowering operational costs. With 35 to 40 percent of the layoffs being in the US, the pharmaceutical industry sector ranked first nationally in the number of job cuts in July 2011 (Wolf (2011) and Wall Street Journal (2011)). Adding to the economic pressures, pharmaceutical companies are expected to suffer a significant decrease in their revenues as a result of losing patent protection for ten of the best-selling drugs by the end of 2012 (De la Garza (2011)). For example, according to Zacks Equity Research (2011), several pharmaceutical products, including Lipitor and Plavix, that, presently, generate more than $142 billion in sales, are expected, over the next five years, to be faced with generic competition. In 2011, pharmaceutical products valued at more than $30 billion lost patent protection, with such products generating more than $15 billion in sales in 2010.

Apart from the cost management pressures and challenges, the safety of imported/outsourced products is another major issue for pharmaceutical companies. In fact, the emergence of counterfeit products has resulted in major reforms in the relationships among various tiers in pharmaceutical supply chains (Dunehew (2005)). Marucheck et al. (2011) noted that, while, in the past, product recalls were mainly related to local errors in design, manufacturing, or labeling, today, a single product safety issue may result in huge global consequences. Interestingly, more than 80% of the ingredients of drugs sold in the US are made overseas, mostly in remote facilities located in China and India that are rarely – if not ever – visited by government inspectors. Supply chains of generic drugs, which account for 75 percent of the prescription medicines sold in the US, are, typically, more susceptible to falsification with the supply chains of some of the over-the-counter products, such as vitamins or aspirins, also vulnerable to adulteration (Harris (2011)). Similarly, the amount of counterfeit drugs in the European pharmaceutical supply chains has considerably increased (Muller et al. (2009)).

Another pressure faced by pharmaceutical firms is the environmental impact of their medical waste, which includes the perished excess medicine, and inappropriate disposal on the retailer/consumer end. Abundant amounts of unused or expired drugs have been found in 41 million American people's drinking water due to improper disposal in domestic trash or in the waste water (Mendoza (2008)).

Note that not all the medical waste generated by healthcare activities are dangerous; rather, only 20% of such waste is considered hazardous material that may be infectious, toxic or radioactive. However, healthcare waste is often not separated into hazardous or non-hazardous wastes, specifically in low-income countries, making the actual volume of hazardous waste much larger (World Health Organization (2011)).

Disruptions of supply chains, particularly in the supplier side, is another challenge faced by the pharmaceutical industries. This is mainly due to fact that a large fraction

of ingredients of drugs are imported/outsourced from overseas the stream of which is vastly vulnerable to natural and man-made disasters.

For instance, when Iraq was invaded by the US, cargo shipments on flights into the US from Singapore were interrupted mainly because the flights from Singapore flew over the Middle East. Consequently, Singapore Airlines had to fly a more southern route and could not carry as much cargo which, in turn, adversely affected the production capacity of certain medication drugs in the US (Craighead et al. (2007)). Therefore, as noted by Qiang, Nagurney, and Dong (2009), the rigorous modeling of supply chain networks in the presence of potential disruptions is imperative since disruptions may have lasting major financial consequences. In conclusion, it is crucial to establish cost-efficient, robust, reliable, safe and sustainable healthcare supply chain systems with a focus on perishable products.

1.2. Literature Review

This literature review begins with a discussion of supply chains of perishable products – Section 1.2.1 – followed by an overview of healthcare product supply chain networks – Section 1.2.2. Then I introduce supply chains associated with various perishable healthcare products, i.e., those in blood and pharmaceuticals – Sections 1.2.3 and 1.2.4, respectively – with the emphasis on the relevant mathematical models.

1.2.1 Perishable Product Supply Chains

Perishable product supply chains have been studied over the past several decades. As mentioned earlier, the study of such supply chain systems poses unique, and, at the same time, complex challenges from various aspects of operations management, network design, inventory management, transportation and storage, etc.

Clearly, not all perishable products are alike and, notably, in some cases, such as that of medicines and vaccines, the quality of a product, or lack thereof, may result in a matter of "life or death" for its consumers.

Due to the limited lifespan of perishable products, several researchers have investigated the problem of inventory tracking, review and ordering policies for such products. Some (e.g., Hwang and Hahn (2000), Omosigho (2002), and Zhou and Yang (2003)) considered the case of a perishable product with a fixed lifetime. Pegels and Jelmert (1970), and Boppana and Chalasani (2007) applied queuing theory to address the inventory management problem for perishable goods. Fujiwara, Soewandi, and Sedarage (1997) presented an optimal ordering policy for a two-stage inventory management system of a perishable product. Sarker, Jamal, and Wang (2000) developed a model to determine an optimal ordering policy for deteriorating items under inflation, a permissible delay of payment and an allowable shortage.

Multiperiod models have also been used to address the ordering, pricing, and inventory problems of perishable products. Nahmias and Pierskalla (1973) and Fries (1975) presented multiperiod ordering models for a perishable product with a fixed lifetime. Nagurney and Aronson (1989) developed a generalized multiperiod spatial price equilibrium model with gains and loses. Cohen, Pierskalla, and Yen (1981) presented an ordering policy model for a product which is differentiated by its age. Bhattacharjee and Ramesh (2000) proposed a heuristic multiperiod solution method for the study of a profit-maximizing firm for both perishable and non-perishable products. Perakis and Sood (2006) and Suryawanshi (2010) developed multiperiod pricing models for a perishable product with fixed inventory using robust optimization approach. In addition, Jia and Hu (2011) constructed a multiperiod pricing model to solve the supply chain of a perishable good consisting of one supplier and a single retailer.

Abad (1996) formulated the pricing and lot-sizing problem of a perishable product reseller, in which backordering was allowed. Burnetas and Smith (2000), Chatwin (2000), Anjos, Cheng, and Currie (2005), Chande et al. (2005), Zhang (2006), and Levin, McGill, and Nediak (2010) discussed the pricing problem for perishable products. In addition, Feng and Xiao (2006) developed an integrated model for the pricing and capacity allocation for perishable products. Moreover, Blackburn and Scudder (2009) developed a cost minimization model for one specific perishable product supply chain design, concerning the declining value of the product over time.

Federgruen, Prastacos, and Zipkin (1986) constructed a combined problem of allocation and distribution of a perishable product from a regional distribution center to a given set of locations with random demands. Entrup (2005) developed mixed-integer linear programming models to integrate the limited shelf life of food into production/processing planning. Yang (2006), in his dissertation, Nagurney and Nagurney (2012), as well as Nagurney, Nagurney, and Li (2012) studied the transportation, the network design, and the sustainability of highly perishable nuclear medicine, respectively.

As for surveys of the literature on general perishable goods supply chains, Wilson (1996) analyzed the results of a qualitative survey of several northern European markets on the distribution and marketing of perishable products. Also, Goyal and Giri (2001), Song, Cai, and Chen (2005), Nahmias (2011), and Karaesmen, Scheller-Wolf, and Deniz (2011) have done comprehensive reviews of the perishable products supply chain management literature.

1.2.2 Healthcare Supply Chains

There has been a surge in the literature related to healthcare supply chains over the past few years. This may be a consequence of various factors among which

the global economic crisis and the inefficiencies of the healthcare systems are most observable.

Similar to other supply chains, the supply chain networks of healthcare products have been studied from different perspectives of cost management, pricing, policy making, distribution and inventory management, etc. Since in the next two sections, i.e., 1.2.3 and 1.2.4, the literature corresponding to two particular instances of healthcare goods are discussed in detail, in this section, I briefly overview more general supply chains of healthcare goods.

Lambert, Adams, and Emmelhainz (1997) investigated supplier selection criteria in the healthcare industry, and concluded that product quality and service rank higher as compared to the price among such criteria. Moalem et al. (2010) developed a supplier selection methodology in a dynamic environment of healthcare providers. Balasubramanian, Muriel, and Wang (2012) applied a two-stage stochastic integer programming approach to investigate the capacity allocation and supplier flexibility for the case of primary case practices.

The flow of information management and information integration throughout the supply chain are other topics of healthcare research. Alshawi, Missi, and Eldabi (2003), Wang, Wang, and Zhu (2005), Blazona and Koncar (2007), and Gong and Chen (2010) are among the researchers to have developed frameworks for healthcare information sharing.

According to a review by Melo, Nickel, and Saldanha da Gama (2009), only a limited number of research papers combine both capacity expansion with locational decisions. Nagurney, Yu, and Qiang (2011) developed a multicriteria system-optimization framework for the distribution of critical needs such as vaccines under uncertain demand with outsourcing. In addition, Qiang and Nagurney (2012) presented a bicriteria measure to assess the robustness of critical needs supply chains under capacity and demand disruptions. The system-optimization approach is believed to be man-

dated for critical supplies (Nagurney, Yu, and Qiang (2011)) in that the demand for such products must be satisfied as closely as possible at minimal total cost.

In the next two sections, I review the literature for two popular instances of perishable healthcare products: that of human blood and pharmaceuticals.

1.2.3 Blood Banking Systems

Blood banking systems, as mentioned earlier, have sparked interest among researchers in perishable goods supply chain problems. Over the past half century, various aspects of blood banks have been examined by operations researchers, engineers, and physicians, and the work is still ongoing.

Millard (1960) seems to have been the first to recognize that inventory management models could be utilized to handle the stocking of whole blood. In the 70s and early 80s, quite a few valuable research publications were carried out that formed the fundamentals of the blood banking supply chain literature. Jennings (1973), Brodheim, Derman, and Prastacos (1975), Or and Pierskalla (1979), Kendall and Lee (1980), Nahmias (1982), and Prastacos (1984) are among the notable earlier contributions to the areas of the transportation and the inventory management of blood products.

Several authors have applied integer optimization models for facility location, set covering, allocation, and routing to address the optimization/design of supply chains of whole blood or other blood products (see Jacobs, Silan, and Clemson (1996), Pierskalla (2004), Yang (2006), Sahin, Sural, and Meral (2007), Sivakumar, Ganesh, and Parthiban (2008), Cetin and Sarul (2009), and Ghandforoush and Sen (2010)).

In addition, inventory management methods (Cohen and Pierskalla (1979), Karaesmen, Scheller-Wolf, and Deniz (2011) and the references therein, and Stanger et al. (2012)) as well as Markov models (Boppana and Chalasani (2007)) have been used to handle blood banking systems.

Some recent studies indicate that transfusing older blood may lead to increased mortality (Price (2011)). Thus, Atkinson et al. (2012) proposed a set of allocation policies that could potentially allow hospitals to reduce the age of transfused blood by allocating the freshest units of blood to the patients of certain illnesses under specific circumstances.

Slonim, Bish, and Xie (2011) and Xie et al. (2011) are among the many to have studied the problem of donated blood screening. Since blood testing is the costliest activity in the blood banking supply chain, they proposed patterns to selectively test particular units of donated blood rather than testing every single donated blood unit. Although the latter is mandated by US federal laws so as to ensure the safety of transfusions, their model could be possibly applied to blood banks in less–developed countries where no systematic testing procedure is being available due to financial issues.

In their survey of the blood banking literature, Belien and Force (2012) admitted that the inherent complexity of finding the optimal policy has resulted in a boost in the number of blood banking publications that have applied simulation techniques. Rytila and Spens (2006), Katsaliaki and Brailsford (2007), Kopach, Balcioglu, and Carter (2008), Mustafee, Katsaliaki, and Brailsford (2009) are among simulation works in the area of blood supply chains. Yegul (2007), in his dissertation, which has extensive references on the subject of blood supply chains, also utilized simulation with a focus on Turkey. He noted that there were few studies which consider multiple echelons. Haijema, van der Wal, and van Dijk (2007), Haijema (2008), and van Dijk et al. (2009) used a Markov dynamic programming and simulation approach with data from Dutch blood banks.

1.2.4 Pharmaceutical Supply Chains

Pharmaceutical supply chains, as other healthcare supply chains, have been assessed from medical, operational, safety and cost perspectives. Papageorgiou, Rotstein, and Shah (2001) developed a commercial pharmaceutical supply chain optimization problem as a mixed integer linear programming model in order to maximize the net present value over a fairly long horizon of interest. Subramanian, Pekny, and Reklaitis (2001) developed an integrated optimization-simulation framework to resolve the uncertainties in the pipeline management problem. Gatica, Papageorgiou, and Shah (2003), Amaro and Barbosa-Povoa (2008), Tsiakis and Papageorgiou (2008), Sousa, Shah, and Papageorgiou (2008), Reimann and Schiltknecht (2009), and Chahed et al. (2009) also applied mixed-integer linear programming techniques to solve various problems of planning, capacity allocation, and distribution of medication drugs.

Shah (2004) expressed that the time to market is a significant motive in the pharmaceutical industry, which secures firms with above the average returns in the early life of a successful drug. Papageorgiou (2009) and Yu et al. (2010) surveyed challenges and methodologies in the area of pharmaceutical supply chains. Rossetti, Handfield, and Dooley (2011) described the complexities of pharmaceutical supply chains based on interviews and text analysis, and provided insights into this industry and its challenges.

Niziolek (2008), in her thesis, applied simulation techniques to study various shipment strategies in medical drug supply networks. Recently, newly-applied technologies in the area of operations of pharmaceutical chains, including RFID-based frameworks, have been studied (see Yue, Wu, and Bai (2008), Schapranow, Zeier, and Plattner (2011), and Cakici, Groenevelt, and Seidmann (2011)).

Nagurney and Nagurney (2012) utilized arc multipliers to capture the perishability/waste of medical nuclear products. Liu and Nagurney (2012a) constructed a

multiperiod supply chain network equilibrium model that captures both perishability of products as well as time delays associated with transportation through the appropriate changes in the underlying network topologies. However, that model did not incorporate arc multipliers and assumed that the product being produced was homogeneous. Nagurney, Yu, and Qiang (2012) developed a centralized framework for the optimization problem of multiproduct humanitarian supply chains.

In addition, various aspects of outsourcing of vaccines and other products have been studied by Boulaksil (2009), Nagurney, Yu, and Qiang (2011), and Liu and Nagurney (2011a) and (2012b). Enyinda (2008) and Enyinda, Briggs, and Bachkar (2009) utilized the analytic hierarchy process to identify optimal strategies for pharmaceutical global supply chains with risk management. Accordingly, Jesson, Pocock, and Wilson (2005) discussed a method of reduction in prescribed medicine with the purpose of minimizing the medical wastage while achieving improved pharmaceutical care standards. See, also, Hernando et al. (2006) and Schwab et al. (2005) for health risk assessment methods associated with pharmaceutical products.

1.3. Dissertation Overview

This dissertation consists of six chapters.

In Chapter 2 of the dissertation, I review the methodologies that are utilized in this dissertation, specifically, variational inequalities, system optimization, multicriteria decision-making, game theory, projected dynamical systems, and the relevant qualitative properties.

In Chapter 3, I formulate the operations management network optimization problem of a blood banking system under centralized (system-optimized) decision-making behavior. I focus on the case of a regional blood bank, as belonging to the American Red Cross, and, through the introduction of generalized arc multipliers, derive the optimization formulation that determines the optimal level of activities on every link in

the network, be it a blood collection, transportation, testing and processing, storage or distribution link. The formulation of the problem is of weighted-sum multicriteria optimization where the two criteria are the minimization of total cost (consisting of total operational cost and total discarding cost of waste) as well as the minimization of supply-side risk inherent in the blood collection links. The demand at the demand points is assumed to be uncertain, while shortage and surplus penalties are assigned in the case of excess demand or excess supply at the demand points.

Note that the use of a profit maximization criterion, as in Nagurney (2010a), is not appropriate for an organization such as, for example, the American Red Cross, due to its non-profit status.

The optimization formulation is then reformulated in terms of its equivalent variational inequality problem which provides nice features for computation. Numerical examples are provided as well as the sensitivity analysis of perishability of blood on supply chain links.

Chapter 4 presents another case of centralized decision-making behavior where the objective is to design/redesign a regional blood banking system so as to minimize the total cost and total supply side-risk while the uncertain demand is satisfied as closely as possible. The solution to the optimization problem not only provides the optimal levels of link activities, but also determines the optimal enhancement/reduction in the capacities of all network activities as well the corresponding shadow prices. Since the proposed system-optimization formulation results in the minimization of the total discarding cost, and, consequently, the minimization of the generated waste, the model is referred to as one of "sustainable network design". Furthermore, the proposed model identifies which links (activities) or nodes (facilities) in the network should possibly be shut down in order to minimize the total cost and risk. Closing of unnecessary arcs/sites, in turn, can lead to a more sustainable system via tremendous amount of reduction in the energy consumption, and the air, water and soil pollution.

In Chapter 5, I transition to the case of decentralized decision-making behavior for the supply chains of another perishable product - that of pharmaceuticals. In contrast to the Chapters 3 and 4, where a system-optimization approach with respect to a single organization was developed, here, I present a network oligopoly model to capture the competition among supply chains of multiple pharmaceutical companies. Moreover, the branding aspect of medical drugs is taken into consideration through product differentiation to address the customers' preference for price, perceived quality, environmental concerns, etc. (See, also, Nagurney and Yu (2012)). In addition, I adopt non-separable total operational cost functions, which capture competition among the firms for resources used in their various supply chain network activities.

Furthermore, the effect of the expiration of patent rights of specific brands on the demand markets is investigated. More specifically, using a case study based on real-world scenarios of a highly popular cholesterol-reducing branded drug, I explore the situation of various demand markets before and shortly after the patent rights of that brand expires which coincides the time when its equivalent generic emerges into the markets. In addition, the case when the demand markets come to stability after the introduction of the newly produced generic drug as well as the competition between the producers of branded and generic substitutes under the new circumstances is examined. The actual observations of the market situation are then compared to that of the predictions. A projected dynamical system (PDS) formulation of the network oligopoly model for pharmaceutical supply chains is also presented.

Finally, Chapter 6 summarizes the obtained results and presents the conclusions. Suggestions and directions for future research are also presented.

CHAPTER 2

METHODOLOGIES

This chapter overviews some of the fundamental methodologies that are utilized in this dissertation. First, variational inequality theory is recalled. Variational inequality theory is the fundamental solution methodology in this dissertation, and is applied in Chapters 3 to 5. It is a powerful methodology that can be used in numerous applications.

After the review of variational inequality theory, I describe the system-optimization approach along with the system-optimality conditions. Such a framework is applied to blood supply chain networks in Chapters 3 and 4. Also, the concepts of multicriteria decision-making and the weighted sum method are briefly discussed to show how these approaches can capture criteria such as the minimization of cost and the risk.

Then, some of the relationships between variational inequalities and game theory are presented. The qualitative properties of the variational inequality model of Nash equilibrium are also recalled.

Finally, finite-dimensional projected dynamical systems – utilized in Chapter 5 – are presented followed by the Euler method which is a computational algorithm that is used in Chapters 3–5 of this dissertation.

2.1. Variational Inequality Theory

In this section, the theory of variational inequalities is recalled. All definitions and theorems are taken from Nagurney (1999) except where noted. We assume that all vectors are column vectors.

Definition 2.1: Variational Inequality

The finite-dimensional variational inequality problem, $\mathrm{VI}(F, \mathcal{K})$*, is to determine a vector* $X^* \in \mathcal{K} \subset R^n$*, such that*

$$\left\langle F(X^*)^T, X - X^* \right\rangle \geq 0, \qquad \forall X \in \mathcal{K}, \tag{2.1}$$

where F *is a given continuous function from* $\mathcal{K}$ *to* R^n*,* $\mathcal{K}$ *is a given closed convex set and* $\left\langle \cdot, \cdot \right\rangle$ *denotes the inner product in n-dimensional Euclidean space, such that*

$$\left\langle F(X^*)^T, X - X^* \right\rangle = \sum_{i=1}^{n} F_i(X^*) \times (X_i - X_i^*). \tag{2.2}$$

Optimization problems, including constrained and unconstrained, can be formulated as variational inequality problems (see Nagurney (1999)). The relationship between variational inequalities and optimization problems, which are utilized in Chapters 3 and 4, is briefly discussed next.

Proposition 2.1

Let X^* *be a solution to the optimization problem:*

$$\textit{Minimize} \quad f(X) \tag{2.3}$$

subject to:

$$X \in \mathcal{K},$$

where f is continuously differentiable and $\mathcal{K}$ is closed and convex. Then X^* is a solution of the variational inequality problem:

$$\langle \nabla f(X^*)^T, X - X^* \rangle \geq 0, \quad \forall X \in \mathcal{K}, \tag{2.4}$$

where $\nabla f(X)$ is the gradient vector of f with respect to X, that is,

$$\nabla f(X) = \begin{pmatrix} \frac{\partial f(X)}{\partial X_1} \\ \frac{\partial f(X)}{\partial X_2} \\ \vdots \\ \frac{\partial f(X)}{\partial X_n} \end{pmatrix}. \tag{2.5}$$

Proposition 2.2

If $f(X)$ is a convex function and X^* is a solution to $\mathrm{VI}(\nabla f, \mathcal{K})$, then X^* is a solution to the optimization problem (2.3). In the case that the feasible set $\mathcal{K} = R^n$, then the unconstrained optimization problem is also a variational inequality problem.

The variational inequality problem can be reformulated as an optimization problem under certain symmetry conditions. The definitions of positive semidefiniteness, positive definiteness, and strongly positive definiteness are presented next, followed by stating the above relationship in a theorem.

Definition 2.2: Positive Semidefinite

An $n \times n$ matrix $M(X)$, whose elements $m_{ij}(X); i, j = 1, ..., n$, are functions defined on the set $\mathcal{S} \subset R^n$, is said to be positive semidefinite on $\mathcal{S}$ if

$$v^T M(X) v \geq 0, \quad \forall v \in R^n, \, X \in \mathcal{S}. \tag{2.6}$$

It is said to be positive definite on $\mathcal{S}$ if

$$v^T M(X) v > 0, \quad \forall v \neq 0, \, v \in R^n, \, X \in \mathcal{S}. \tag{2.7}$$

It is said to be strongly positive definite on $\mathcal{S}$ *if*

$$v^T M(X)v \geq \alpha \|v\|^2, \text{ for some } \alpha > 0, \quad \forall v \in R^n, X \in \mathcal{S}. \tag{2.8}$$

Theorem 2.1

Assume that $F(X)$ *is continuously differentiable on* $\mathcal{K}$ *and that the Jacobian matrix*

$$\nabla F(X) = \begin{bmatrix} \frac{\partial F_1}{\partial X_1} & \cdots & \frac{\partial F_1}{\partial X_n} \\ \vdots & \cdots & \vdots \\ \frac{\partial F_n}{\partial X_1} & \cdots & \frac{\partial F_n}{\partial X_n} \end{bmatrix} \tag{2.9}$$

is symmetric and positive semidefinite. Then there is a real-valued convex function $f : \mathcal{K} \longmapsto R^1$ *satisfying*

$$\nabla f(X) = F(X) \tag{2.10}$$

with X^* *the solution of* $\mathrm{VI}(F, \mathcal{K})$ *also being the solution of the mathematical programming problem:*

$$\textit{Minimize} \quad f(X)$$

subject to:

$$X \in \mathcal{K},$$

where $f(X) = \int F(X)^T dx$, *and* $\int$ *is a line integral.*

Therefore, the variational inequality is a more general problem formulation, which can also handle a function $F(X)$ with an asymmetric Jacobian (see Nagurney (1999)).

Next, the qualitative properties of variational inequality problems, especially the conditions for existence and uniqueness of a solution are presented.

Theorem 2.2

If $\mathcal{K}$ *is a compact convex set and* $F(X)$ *is continuous on* $\mathcal{K}$, *then variational inequality (2.1) admits at least one solution* X^*.

Theorem 2.3

If the feasible set $\mathcal{K}$ is unbounded, then $\mathrm{VI}(F, \mathcal{K})$ *admits a solution if and only if there exists an $\mathcal{R} > 0$ and a solution of* $\mathrm{VI}(F, \mathcal{S})$, X_R^*, *such that $\|X_R^*\| < \mathcal{R}$, where $\mathcal{S} = \{X : \|X\| \leq \mathcal{R}\}$.*

Theorem 2.4

Suppose that $F(X)$ satisfies the coercivity condition

$$\frac{\langle (F(X) - F(X_0))^T, X - X_0 \rangle}{\|X - X_0\|} \to \infty \tag{2.11}$$

as $\|X\| \to \infty$ for $X \in \mathcal{K}$ and for some $X_0 \in \mathcal{K}$. Then $\mathrm{VI}(F, \mathcal{K})$ *always has a solution.*

A few basic definitions are now recalled.

Definition 2.3: Monotonicity

$F(X)$ is monotone on $\mathcal{K}$ if

$$\langle (F(X^1) - F(X^2))^T, X^1 - X^2 \rangle \geq 0, \quad \forall X^1, X^2 \in \mathcal{K}. \tag{2.12}$$

Definition 2.4: Strict Monotonicity

$F(X)$ is strictly monotone on $\mathcal{K}$ if

$$\langle (F(X^1) - F(X^2))^T, X^1 - X^2 \rangle > 0, \quad \forall X^1, X^2 \in \mathcal{K},\ X^1 \neq X^2. \tag{2.13}$$

Definition 2.5: Strong Monotonicity

$F(X)$ is strongly monotone on $\mathcal{K}$ if

$$\langle (F(X^1) - F(X^2))^T, X^1 - X^2 \rangle \geq \alpha \|X^1 - X^2\|^2, \quad \forall X^1, X^2 \in \mathcal{K}, \tag{2.14}$$

where $\alpha > 0$.

Definition 2.6: Lipschitz Continuity

$F(X)$ is Lipschitz continuous on $\mathcal{K}$ if there exists an $L > 0$, known as the Lipschitz constant, such that

$$\langle (F(X^1) - F(X^2))^T, X^1 - X^2 \rangle \leq L\|X^1 - X^2\|^2, \quad \forall X^1, X^2 \in \mathcal{K}. \tag{2.15}$$

Theorem 2.5

Suppose that $F(X)$ is strictly monotone on $\mathcal{K}$. Then the solution to the VI$(F, \mathcal{K})$ *problem is unique, if one exists.*

Theorem 2.6

Suppose that $F(X)$ is strongly monotone on $\mathcal{K}$. Then there exists precisely one solution X^* to VI$(F, \mathcal{K})$.

From Theorems 2.2, 2.5 and 2.6, one has the following conclusions. In the case of an unbounded feasible set $\mathcal{K}$, strong monotonicity of the function F guarantees both existence and uniqueness. If the feasible set $\mathcal{K}$ is compact, that is, closed and bounded, then the continuity of F guarantees the existence of a solution. Finally, strict monotonicity of F is sufficient to guarantee the uniqueness of a solution X^* provided that a solution exists.

2.2. The System-Optimization Model

In this section the system-optimized (S-O) problem – which is in contrast to the user-optimized (U-O) problem – is recalled. The S-O approach is utilized in Chapters 3 and 4 of this dissertation to handle the problems of the management and the design of blood banking systems. The S-O problem is a classic network optimization problem and originates in the context of transportation problems (see Dafermos and Sparrow (1969) and Dafermos (1971)). It is necessary to mention that the equations presented

in this chapter relate to a general (non-perishable) product where in the following chapters the perishability of a product is added.

Consider a network G with the set of nodes N, the set of links L with n_L elements, the set of paths $\mathcal{P}$ with n_P elements, and the set of origin/destination (O/D) pairs of nodes W with n_W elements. Let P_w denote the set of (acyclic) paths connecting O/D pair w. Links are denoted by a, b, etc.; the paths by p, q, etc., and the O/D pairs by w_1, w_2, etc. Furthermore, x_p and f_a denote the flow on path p and link a, respectively. x denotes the vector of all path flows and f denotes the vector of all link flows. The demand associated with O/D pair w is denoted by d_w and is assumed to be known and fixed.

The following conservation of flow equations must hold for all O/D pairs $w \in W$:

$$d_w = \sum_{p \in P_w} x_p, \tag{2.16}$$

that is, the demand associated with each O/D pair is equal to the summation of all path flows connecting that origin to its destination.

In addition, the following conservation of flow equations relate the link flows to the path flows:

$$f_a = \sum_{p \in \mathcal{P}} x_p \delta_{ap}, \quad \forall a \in L, \tag{2.17}$$

where $\delta_{ap} = 1$, if path p contains link a, and $\delta_{ap} = 0$, otherwise. In other words, the flow on a link is equal to the sum of the flows of paths that contain that link.

Another set of equations is required to guarantee the non-negativity of path flows, that is,

$$x_p \geq 0, \quad \forall p \in \mathcal{P}. \tag{2.18}$$

Let c_a denote the user cost on link a. The user link cost functions are assumed to be continuous and continuously differentiable. For the sake of generality, the user cost on a link is assumed to be a function of all the link flows, f, so that

$$c_a = c_a(f), \quad \forall a \in L. \tag{2.19}$$

Accordingly, the total cost on link a, denoted by $\hat{c}_a$, can be expressed as:

$$\hat{c}_a(f) = c_a(f) \times f_a, \quad \forall a \in L, \tag{2.20}$$

that is, the total cost of a link is equal to the user cost on the link times the flow on the link.

Let C_p denote the user (individual) cost on a path p, where

$$C_p = \sum_{a \in L} c_a \delta_{ap}, \quad \forall p \in \mathcal{P}. \tag{2.21}$$

Then, the total cost on path p, denoted by $\hat{C}_p$ can be calculated as:

$$\hat{C}_p(x) = C_p \times x_p, \quad \forall p \in \mathcal{P}. \tag{2.22}$$

In contrast to the user-optimized problem where every single user aims to minimize his/her individual cost, in the system-optimized problem, a central controller is assumed to route the flows in an optimal manner so as to minimize the total cost in the network. The total cost of the network, denoted by TC, is defined as:

$$TC = \sum_{a \in L} \hat{c}_a(f). \tag{2.23}$$

The S-O problem, thus, can be expressed as:

$$\text{Minimize} \quad TC = \sum_{a \in L} \hat{c}_a(f), \tag{2.24}$$

subject to constraints (2.16)-(2.18).

Let K^1 denote the feasible set such that

$$K^1 \equiv \{f | (2.16) - (2.18) \text{ are satisfied}\}. \tag{2.25}$$

Equivalently, the S-O problem with objective function (2.24) can be re-expressed in terms of path flows utilizing the user costs on paths, as follows:

$$\text{Minimize} \quad \sum_{p \in \mathcal{P}} C_p(x) \times x_p, \tag{2.26}$$

subject to constraints (2.16) and (2.18).

The feasible set of the latter S-O problem, denoted by K^2, is

$$K^2 \equiv \{x | (2.16) \text{ and } (2.18) \text{ are satisfied}\}. \tag{2.27}$$

The objective function (2.24) in the S-O problem is convex, based upon the assumption of increasing user link cost functions. The feasible set K^1 is also convex. Hence, the system–optimality conditions correspond to the Kuhn-Tucker conditions (Bazaraa, Sherali, and Shetty (1993)).

2.2.1 The System-Optimality Conditions

Under the assumption of increasing user link cost functions, a convex objective function in the S-O problem, and a convex feasible set consisting of linear constraints, the optimality conditions, that is, the Kuhn-Tucker conditions are as follows (Beckmann, McGuire, and Winsten (1956) and Dafermos and Sparrow (1969)):

For each O/D pair $w \in W$ and each path $p \in P_w$, the path flow pattern x (and the corresponding link flow patter f), satisfying constraints (2.16)-(2.18), must satisfy:

$$\hat{C}'_p(x) \begin{cases} = \mu_w, & \text{if} \quad x_p > 0, \\ \geq \mu_w, & \text{if} \quad x_p = 0, \end{cases} \tag{2.28}$$

where $\hat{C}'_p(x)$ denotes the marginal of the total cost on path p, and is defined as:

$$\hat{C}'_p(x) \equiv \sum_{a \in L} \sum_{b \in L} \frac{\partial \hat{c}_b(f)}{\partial f_a} \delta_{ap}, \tag{2.29}$$

evaluated in (2.28) at the solution and μ_w is the Lagrange multiplier associated with constraint (2.16) for that O/D pair w.

Based on the optimality conditions (2.28), in the S-O problem, the marginal of the total cost on each used path connecting an O/D pair is equalized and minimal (see also, e.g., Dafermos and Sparrow (1969) and Dafermos (1971)).

2.3. Multicriteria Decision-Making

The purpose of multicriteria decision-making (MCDM) is to evaluate a set of alternatives in terms of a number of possibly conflicting criteria (Keeney and Raiffa (1976) and Cohon (1978)), according to the preferences of the decision-maker (Gal, Stewart, and Hanne (1999), and Jones, Mirrazavi, and Tamiz (2002)). Multicriteria decision–making theory is utilized in Chapters 3 and 4 to capture such criteria as total cost and total supply-side risk. In this section, the problem of multicriteria optimization and the weighted sum method are briefly reviewed.

The multicriteria optimization problem with n decision variables, can be generalized as (see Marler and Arora (2004)):

$$\text{Minimize} \quad \mathbf{F}(x) = [F_1(x), F_2(x), \ldots, F_k(x)]^{\mathsf{T}} \tag{2.30}$$

subject to:

$$g_j(x) \leq 0, \quad j = 1, 2, \ldots, m, \tag{2.31}$$

$$h_l(x) = 0, \quad l = 1, 2, \ldots, e, \tag{2.32}$$

where k is the number of objective functions, m is the number of inequality constraints, e is the number of equality constraints, and x is the n-dimensional vector of decision variables. The feasible set K is defined as:

$$K \equiv \{x | (2.31) \text{ and } (2.32) \text{ are satisfied}\}. \tag{2.33}$$

Next, the concept of Pareto-optimality of a solution to a multicriteria problem, defined by Pareto (1971), is recalled.

Definition 2.7: Pareto Optimal

A point, $x^* \in K$, is Pareto optimal iff there does not exist another point, $x \in K$, such that $\mathbf{F}(x) \leq \mathbf{F}(x^*)$, and $\mathbf{F}_i(x) < \mathbf{F}_i(x^*)$ for at least one function.

The weighted sum method is the most common approach to multicriteria optimization problems (Marler and Arora (2004)). Associated with a vector of weights, denoted by w, representing the decision maker's preferences, the multicriteria objective function (2.30) can be expressed as:

$$U = \sum_{i=1}^{k} w_i F_i(x). \tag{2.34}$$

As noted by Zadeh (1963), the optimal solution to (2.34) is Pareto optimal if all of the weights are positive.

2.4. The Relationships between Variational Inequalities and Game Theory

In this section, I briefly recall the relationship between variational inequalities and game theory. The definitions and the relationships presented here are utilized in Chapter 5 of this dissertation to capture the competition among the firms in the pharmaceutical oligopoly problem.

Nash (1950, 1951) developed noncooperative game theory, involving multiple players, each of whom acts in his/her own interest. In particular, consider a game with m players, each player i having a strategy vector $X_i = \{X_{i1}, ..., X_{in}\}$ selected from a closed, convex set $\mathcal{K}^i \subset R^n$. Each player i seeks to maximize his/her own utility function, U_i: $\mathcal{K} \longmapsto R$, where $\mathcal{K} = \mathcal{K}^1 \times \mathcal{K}^2 \times \ldots \times \mathcal{K}^m \subset R^{mn}$. The utility of player i, U_i, depends not only on his/her own strategy vector, X_i, but also on the strategy vectors of all the other players, $(X_1, \ldots, X_{i-1}, X_{i+1}, \ldots, X_m)$. An equilibrium is achieved if no one can increase his/her utility by unilaterally altering the value of its strategy vector. The formal definition of Nash equilibrium is:

Definition 2.8: Nash Equilibrium

A Nash equilibrium is a strategy vector

$$X^* = (X_1^*, \ldots, X_m^*) \in \mathcal{K}, \tag{2.35}$$

such that

$$U_i(X_i^*, \hat{X}_i^*) \geq U_i(X_i, \hat{X}_i^*), \quad \forall X_i \in \mathcal{K}^i, \forall i, \tag{2.36}$$

where $\hat{X}_i^* = (X_1^*, \ldots, X_{i-1}^*, X_{i+1}^*, \ldots, X_m^*)$.

In other words, under Nash equilibrium, no unilateral deviation in strategy by any single player makes her better off.

Given continuously differentiable and concave utility functions, U_i, $\forall i$, the Nash equilibrium problem can be formulated as a variational inequality problem defined on $\mathcal{K}$ (cf. Hartman and Stampacchia (1966) and Gabay and Moulin (1980)).

Theorem 2.7: Variational Inequality Formulation of Nash Equilibrium

Under the assumption that each utility function U_i is continuously differentiable and concave, X^* is a Nash equilibrium if and only if $X^* \in \mathcal{K}$ is a solution of the variational inequality

$$\langle F(X^*)^T, X - X^* \rangle \geq 0, \quad X \in \mathcal{K}, \tag{2.37}$$

where $F(X) \equiv (-\nabla_{X_1} U_1(X), \ldots, -\nabla_{X_m} U_m(X))^T$ and
$\nabla_{X_i} U_i(X) = (\frac{\partial U_i(X)}{\partial X_{i1}}, \ldots, \frac{\partial U_i(X)}{\partial X_{in}})$.

In the next four theorems, the conditions for existence and uniqueness of a Nash equilibrium are provided. Rosen (1965) presented existence under the assumptions that $\mathcal{K}$ is compact and each U_i is continuously differentiable.

Theorem 2.8: Existence under Compactness and Continuous Differentiability

Suppose that the feasible set $\mathcal{K}$ is compact and U_i is continuously differentiable, for each player i. Then the existence of a Nash equilibrium is guaranteed.

Gabay and Moulin (1980) proved the existence of a Nash equilibrium after imposing a coercivity condition on $F(X)$, without the requirement of compactness of $\mathcal{K}$.

Theorem 2.9: Existence under Coercivity

Suppose that $F(X)$, as given in Theorem 2.7, satisfies the coercivity condition (2.11). Then there always exists a Nash equilibrium.

Under the strong monotonicity assumption, Karamardian (1969) demonstrated both existence and uniqueness of a Nash equilibrium.

Theorem 2.10: Existence and Uniqueness Under Strong Monotonicity

Assume that $F(X)$, as given in Theorem 2.7, is strongly monotone on $\mathcal{K}$. Then there exists precisely one Nash equilibrium X^*.

Moreover, a Nash equilibrium is guaranteed to have a unique solution under the assumptions that $F(X)$ is strictly monotone and an equilibrium exists, based on Theorem 2.5.

Theorem 2.11: Uniqueness Under Strict Monotonicity

Suppose that $F(X)$, as given in Theorem 2.7, is strictly monotone on $\mathcal{K}$. Then the Nash equilibrium, X^*, is unique, if it exists.

2.5. Finite-Dimensional Projected Dynamical Systems

In this section, the definitions of several fundamental terms associated with a projected dynamical systems (PDS) are recalled (cf. Dupuis and Nagurney (1993), Nagurney and Zhang (1996)). I follow with a discussion on the relationship between finite-dimensional projected dynamical systems and finite-dimensional variational inequalities. All the definitions and theorems can be found in Nagurney and Zhang (1996), except where noted.

Definition 2.9: Vector Projection

Given $X \in \mathcal{K}$ and $v \in R^n$, define the projection of the vector v at X (with respect to $\mathcal{K}$) by

$$\Pi_{\mathcal{K}}(X, v) = \lim_{\delta \to 0} \frac{(P_{\mathcal{K}}(X + \delta v) - X)}{\delta}, \tag{2.38}$$

where $P_{\mathcal{K}}$ is the norm projection defined by

$$P_{\mathcal{K}}(X) = \text{argmin}_{X' \in \mathcal{K}} \|X' - X\|. \tag{2.39}$$

The class of ordinary differential equations in this dissertation will take on the form:

$$\dot{X} = \Pi_{\mathcal{K}}(X, -F(X)), \quad X(0) = X_0 \in \mathcal{K}, \tag{2.40}$$

where $\dot{X}$ denotes the rate of change of the vector X, $\mathcal{K}$ is a closed convex set, corresponding to the constraint set in a particular application, and $F(X)$ is a vector field defined on $\mathcal{K}$.

The classical dynamical system, in contrast to (2.40), is of the form:

$$\dot{X} = -F(X), \quad X(0) = X_0 \in \mathcal{K}. \tag{2.41}$$

Definition 2.10: The Finite-Dimensional Projected Dynamical System

Define the finite-dimensional projected dynamical system PDS $(F, \mathcal{K})$ *such that* $X_0(t) : \mathcal{K} \times R \longmapsto \mathcal{K}$ *is the family of solutions to the Initial Value Problem (IVP) (2.40) for all* $X_0 \in \mathcal{K}$.

Definition 2.11: Equilibrium (Stationary) Point

The vector $X^* \in \mathcal{K}$ *is an equilibrium (stationary) point of the finite-dimensional* PDS$(F, \mathcal{K})$ *if*

$$0 = \Pi_{\mathcal{K}}(X^*, -F(X^*)). \tag{2.42}$$

In other words, X^* is a stationary point if, once the projected dynamical system is at X^*, it will remain there at any point of time in the future. This definition states that X^* is a stationary point of the finite-dimensional projected dynamical system PDS$(F, \mathcal{K})$ if the projection of the vector field F on the feasible set $\mathcal{K}$ vanishes at X^*. In the case that X^* lies on the boundary of $\mathcal{K}$, one may have $F(X^*) \neq 0$. The contrary is only true when X^* is an interior point of the constraint set $\mathcal{K}$. For classical dynamical systems, the necessary and sufficient condition for an equilibrium point X^* is that $0 = -F(X^*)$.

Next, I present a theorem (see Dupuis and Nagurney (1993)) that establishes the equivalence between the set of equilibria of a PDS and the set of solutions of a variational inequality problem.

Theorem 2.12

Assume that $\mathcal{K}$ is a convex polyhedron. Then the set of equilibrium points (cf.(2.42)) of the finite-dimensional PDS$(F, \mathcal{K})$ *coincides with the set of solutions of the finite-dimensional* VI$(F, \mathcal{K})$ *problem in (2.1). Therefore, $X^* \in \mathcal{K}$ satisfies*

$$0 = \Pi_{\mathcal{K}}(X^*, -F(X^*)), \tag{2.43}$$

and

$$\langle F(X^*)^T, X - X^* \rangle \geq 0, \quad \forall X \in \mathcal{K}. \tag{2.44}$$

Now I provide conditions for existence and uniqueness of the trajectory of the finite-dimensional PDS.

Theorem 2.13

Assume that there exists a $B < \infty$ such that the vector field $F : R^n \longmapsto R^n$ satisfies the linear growth condition: $\|F(X)\| \leq B(1 + \|X\|)$ for $X \in \mathcal{K}$, and also

$$\langle (-F(X^1) + F(X^2))^T, X^1 - X^2 \rangle \leq B\|X^1 - X^2\|^2, \quad \forall X^1, X^2 \in \mathcal{K}, \tag{2.45}$$

then

(1) for any $X_0 \in \mathcal{K}$, there exists a unique solution $X_0(t)$ to the IVP

$$\dot{X} = \Pi_{\mathcal{K}}(X, -F(X)), \quad X(0) = X_0; \tag{2.46}$$

(2) if $X_k \to X_0$ as $k \to \infty$, then $X_k(t)$ converges to $X_0(t)$ uniformly on every compact set of $[0, \infty)$.

The second part of this theorem is also referred to as the continuous dependence of the solution path to the ODE$(F, \mathcal{K})$ on the initial value.

For completeness, I now recall the definition of stability of the system (Nagurney and Zhang (1996)).

Definition 2.12: Stability of the System

The system defined by equation (2.46) *is stable if, for every* X_0 *and every equilibrium point* X^**, the Euclidean distance* $\|X^* - X_0(t)\|$ *is a monotonically non-increasing function of time* t*.*

2.6. The Euler Method

In this section, the Euler method is presented for the computation of solutions to finite-dimensional projected dynamical systems (2.40). The algorithm is induced by the general iterative scheme of Dupuis and Nagurney (1993). The Euler method provides a discretization of the continuous time trajectory defined in (2.42). At iteration $\tau + 1$ the procedure takes the form:

$$X^{\tau+1} = P_{\mathcal{K}}[X^{\tau} - \alpha_{\tau} F(X^{\tau})], \tag{2.47}$$

where $P_{\mathcal{K}}$ denotes the operator of projection (cf.(2.39)) onto the closed convex feasible set $\mathcal{K}$.

I now provide the complete statement of the Euler method.

Step 0: Initialization

Set $X^0 \in \mathcal{K}$.

Let $\tau = 1$ and set the sequence $\{\alpha_\tau\}$ so that $\sum_{\tau=1}^{\infty} \alpha_\tau = \infty, \alpha_\tau > 0$ for all τ, and $\alpha_\tau \to 0$ as $\tau \to \infty$.

Step 1: Computation

Compute $X^{\tau} \in \mathcal{K}$ by solving the variational inequality subproblem:

$$\langle X^{\tau} + \alpha_{\tau} F(X^{\tau-1}) - X^{\tau-1}, X - X^{\tau} \rangle \geq 0, \quad \forall X \in \mathcal{K}. \tag{2.48}$$

Step 2: Convergence Verification

If $|X^{\tau} - X^{\tau-1}| \leq \epsilon$, with $\epsilon > 0$ a pre-specified tolerance, then stop; otherwise, set $\tau := \tau + 1$, and go to Step 1.

As shown in Dupuis and Nagurney (1993); see also Nagurney and Zhang (1996), for convergence of the general iterative scheme, which induces the Euler method, among other methods, the sequence $\{a_{\tau}\}$ must satisfy: $\sum_{\tau=1}^{\infty} a_{\tau} = \infty$, $a_{\tau} > 0$, $a_{\tau} \rightarrow 0$, as $\tau \rightarrow \infty$. Specific conditions for convergence of this scheme can be found for a variety of network-based problems, similar to those constructed in this dissertation, in Nagurney and Zhang (1996) and the references therein.

This concludes Chapter 2 of this dissertation. In the following chapters, I derive the variational inequality formulations of the supply chain network models for perishable products and adapt the computational algorithm accordingly.

CHAPTER 3

SUPPLY CHAIN NETWORK OPERATIONS MANAGEMENT OF A BLOOD BANKING SYSTEM WITH COST AND RISK MINIMIZATION

In this chapter, I develop a supply chain network model for the study of the procurement and distribution of a perishable product, in general, and of human blood, in particular. More specifically, I present a generalized network optimization model for a regionalized blood banking system consisting of collection sites, testing and processing facilities, storage facilities, distribution centers, as well as points of demand. The multicriteria system-optimization approach on generalized networks with arc multipliers captures many of the critical issues associated with blood supply chains such as the determination of the optimal allocations, and the induced supply-side risk, as well as the induced cost of discarding the waste, while satisfying the uncertain demands as closely as possible.

This chapter is based on Nagurney, Masoumi, and Yu (2012). The organization of this chapter is as follows. In Section 3.1, the structure of a regionalized blood banking system is described followed by the presentation of the supply chain network model for the blood banking system problem. I establish that the multicriteria optimization problem is equivalent to a variational inequality problem, with nice features for computations. In 3.2, I present illustrative numerical examples and conduct sensitivity analysis to examine the effect of perishability throughout the supply chain network. In Section 3.3, I propose an algorithm which computes the optimal level of blood product flows. Next, I apply the algorithm to compute the solution to a larger-scale numerical example using data motivated by a real-world application in

order to further illustrate the modeling and computational framework. In Section 3.4, I summarize the results and present my conclusions.

3.1. The Supply Chain Network Model of a Regionalized Blood Banking System

In this section, I develop the supply chain network model for regionalized blood banks. It is necessary to mention that the model for blood banking management is applicable to many perishable products, with minor modifications, but with the same foundations. Also, it is worth noting that although the structure of the network for a blood banking system, or the way that the modules of the supply chain are called, may be slightly different from country to country, or from one region to another, this network framework is sufficiently general to address any blood supply chain network.

3.1.1 The Components of a Regionalized Blood Banking System

In most parts of the world, blood banking operations systems conduct procurement and distribution in a regionalized manner. In other words, there exists a *Regional Blood Center* in each geographic area which is in charge of the coordination and administration of its lower-level units. Nevertheless, despite advances in storage and distribution technologies, hospitals may need to acquire blood products from suppliers that are located in other regions, sometimes even hundreds of miles away.

In the US, for example, the regional divisions of the American Red Cross (ARC) oversee the entire operation of their corresponding regions. Other suppliers of blood are hospitals – typically the larger ones with blood collection programs – which, however, account for less than 5% of the market share (Whitaker et al. (2007)). There also exist private blood suppliers across the country.

Since 1960, the Red Cross has been reimbursed by the hospitals for the costs associated with providing blood to hospital patients. The Red Cross does not charge

for the blood itself; it only recovers the costs associated with the recruitment and screening of potential donors, the collection of blood by trained staff, the processing and testing of each unit of blood in state-of-the-art laboratories, and the labeling, storage, and distribution of blood components.

Figure 3.1 depicts a network topology of a regionalized blood banking system for the ARC in the US. In this network, the top level (origin) node represents the ARC regional division. Every other node in the network denotes a component/facility in the system. A path connecting the origin node to a destination node, corresponding to a demand point, consists of a sequence of directed links which correspond to supply chain network activities that ensure that the blood is collected, processed, and, ultimately, distributed to the demand point. I assume that in the supply chain network topology there exists at least one path joining node 1 with each destination node. This assumption guarantees that the demand at each demand point will be met as closely as possible, given that I am considering uncertain demand for blood at each demand point. The solution of the model yields the optimal flows of blood at minimum total cost and risk.

In the network in Figure 3.1, the division is considering n_{CS} *blood collection sites* constituting the second tier of the network. Many of these collection sites are mobile or temporary locations while others are permanent sites. In the case of drastic shortages; i.e., natural or man-made disasters, the regional divisions are likely to need to import blood products from other regions or even other countries, an aspect that is excluded from this model. In the current topology, the first set of the links connecting the origin node to the second tier corresponds to the process of "blood collection." These collection sites are denoted by: $CS_1, CS_2, \ldots, CS_{n_{CS}}$.

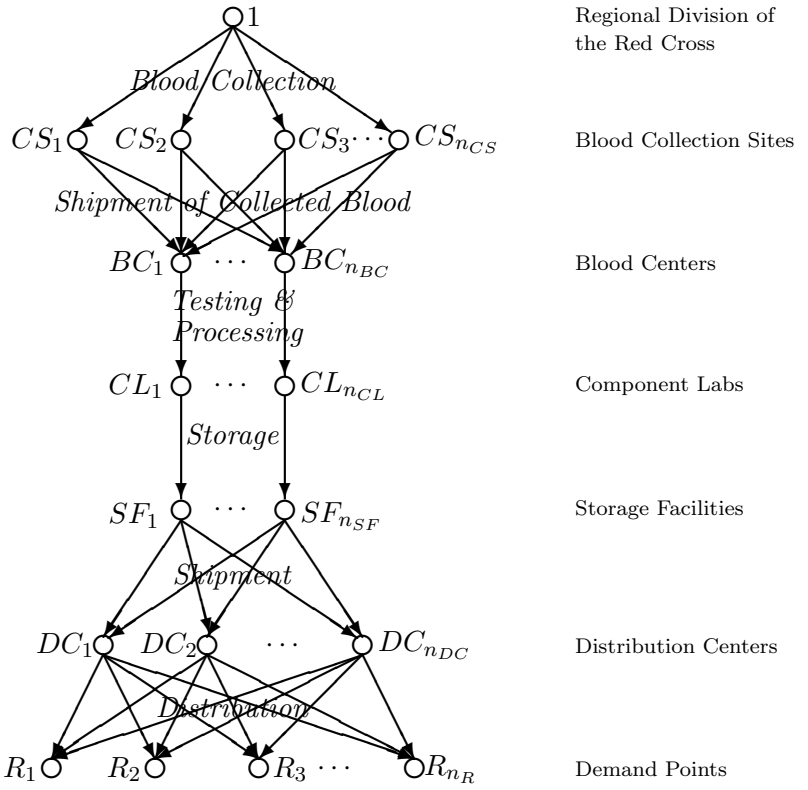

Figure 3.1. Supply Chain Network Topology for A Regionalized Blood Bank

The next set of nodes, located in the third tier, consists of the *blood centers*. There exist n_{BC} of these facilities in one region, denoted by $BC_1, BC_2, \ldots, BC_{n_{BC}}$, to which the whole blood (WB) is shipped after being collected at the collection sites. Thus, the next set of links connecting tiers two and three of the network topology represents the "shipment of collected blood."

The fourth tier of the network is composed of processing facilities, commonly referred to as *component labs*. The number of these facilities in one region is assumed to be n_{CL}. These facilities are denoted by $CL_1, \ldots, CL_{n_{CL}}$, respectively, and are typically located within the blood center locations. At these labs, the collected blood is separated into parts, i.e., red blood cells and plasma, since most recipients need

only a specific component for transfusions. Every unit of donated whole blood – 450 to 500 milliliters on average – can provide one unit of red blood cells (RBC) and one unit of plasma. What I refer to as the flow of product is the amount of whole blood (WB) on the first three sets of links. Likewise, the flow on the links thereafter denotes the number of units of red blood cells (RBC) processed at the component labs which are, ultimately, delivered to the hospitals.

Plasma and other side derivatives are excluded for several reasons. Although plasma can be derived from donated whole blood, in practice, plasma is mainly produced in a different process called *apheresis*. Apheresis is a blood donation method where the blood is passed through an apparatus that separates out one particular constituent – plasma – and returns the remainder – red blood cells – to the donor. Secondly, plasma can be stored frozen for an extended period of time, typically one year, which is not comparable to the approximately 5 week lifetime of red blood cells. Most important of all, whole blood and red blood cells account for the major part of donations and transfusions rather than plasma and other components (Whitaker et al. (2007)).

The safety of the blood supply is considered to be the most important issue in blood services. In the US, federal law mandates that every single unit of donated blood be tested before being transfused, regardless of the number of the times one donor has donated blood in the past. The *National Testing Laboratories* of the American Red Cross are in charge of this vital task, testing blood for multiple infectious disease markers, including but not limited to HIV, hepatitis, and the West Nile Virus (Redcrossblood.org (2010)). These facilities are owned and operated by the ARC, and require heavy investments for specialized equipment. Presently, only 5 testing labs are operating across the US, and these labs are shared among 36 blood regions. Only a small sample of every donated blood unit is sent to the testing labs, overnight, and these samples are discarded regardless of the results of the tests. Due to the high

perishability of many of the blood products, the two processes of testing and separating take place concurrently yet sometimes hundreds of miles away. If the result of a test for a specific unit of donated blood at the testing lab turns out to be positive, the remainder of that unit will be later discarded at the corresponding storage facility. In the model, the set of the links connecting the component labs to storage facilities corresponds to "testing and processing", and the cost on these links represents the operational cost of testing and processing combined. The fraction of the flow lost during or as a result of the testing process is also taken care of in this model.

The fifth set of nodes denotes the short-term *storage facilities*. There are n_{SF} of such nodes in the network, denoted by $SF_1, SF_2, \ldots, SF_{n_{SF}}$, which are usually located in the same place as the component labs. The links connecting the upper level nodes to the storage facilities denote the procedure of "storage" of the tested and processed blood before it is shipped to be distributed.

The next set of nodes in the network represents the *distribution centers*, denoted by $DC_1, DC_2, \ldots, DC_{n_{DC}}$, where n_{DC} is the total number of such facilities in the region. Distribution centers act as transshipment nodes, and are in charge of facilitating the distribution of blood to the ultimate destinations. The links connecting the storage tier to the distribution centers are of "shipment" link type.

The last set of links joining the bottom two tiers of the network are "distribution" links, ending in n_R *demand points*. Hospitals and surgical medical centers are the predominant users of blood. The actual but uncertain demands of the demand points $R_1, R_2, \ldots, R_{n_R}$ are denoted by: $d_{R_1}, d_{R_2}, \ldots, d_{R_{n_R}}$, respectively.

It is necessary to mention that specific components of the system may physically coincide with some others; this network topology is process-based rather than location-based, which is compatible with the real-world blood banking problems. Moreover, as mentioned earlier, in general cases of perishable product supply chains,

these facilities may be located far apart which can be nicely addressed using the model.

The supply chain network topology is represented by $G = [N, L]$, where N and L denote the sets of nodes and links, respectively. The ultimate solution of the complete model will yield the optimal flow on the various links of the network.

3.1.2 The Formulation of Supply Chain Network Model of a Regionalized Blood Banking System

The formulation of the model is of a single-period type, where the time horizon spans the various activities of procurement, processing, and distribution. Since whole blood is highly perishable, all modules of the blood supply chain network tend to avoid long term storage (except for plasma, which is excluded from my model). Hence, the assumption of a single-period time horizon is realistic with the focus of this model being on operations management, rather than on inventory management. Nevertheless, this model takes into account the potential shortage associated with the uncertain demand at the demand points, that is, the lost "sales." In addition, the surplus penalty can address additional relevant costs, whether in terms of excess supply or even if short-term inventory holding cost is included.

Associated with each link of the network is a unit operational cost function that reflects the cost of operating the particular supply chain activity, that is, the collection of blood at blood drive sites, the shipment of collected blood, the testing and processing, the storage, and the distribution. Denote these links by a, b, etc. The unit operational cost on link a is denoted by c_a and is a function of flow on that link, f_a. The *total* operational cost on link a is denoted by $\hat{c}_a$, and is constructed as:

$$\hat{c}_a(f_a) = f_a \times c_a(f_a), \qquad \forall a \in L. \tag{3.1}$$

The link total cost functions are assumed to be convex and continuously differentiable.

The origin/destination (O/D) nodes consist of the pairs of nodes $(1,\ R_k)$; $k = 1, \ldots, n_R$, where $\mathcal{P}_k$ denotes the set of paths, which represent alternative associated possible supply chain network processes, joining $(1,\ R_k)$. $\mathcal{P}$ denotes the set of all paths joining node 1 to the destination nodes, and $n_{\mathcal{P}}$ denotes the number of paths.

Let v_k denote the *projected demand* for blood at the demand point $R_k; k = 1, \ldots, n_R$. Assume that the demand at each demand point is uncertain with a known probability distribution. Let d_k denote the actual demand at demand point $R_k; k = 1, \ldots, n_R$, which is a random variable with probability density function given by $\mathcal{F}_k(t)$. Let P_k be the probability distribution function of d_k, that is, $P_k(D_k) = Probability(d_k \leq D_k) = \int_0^{D_k} \mathcal{F}_k(t)dt$. Hence,

$$\Delta_k^- \equiv \max\{0, d_k - v_k\}, \qquad k = 1, \ldots, n_R, \tag{3.2}$$

$$\Delta_k^+ \equiv \max\{0, v_k - d_k\}, \qquad k = 1, \ldots, n_R, \tag{3.3}$$

where Δ_k^- and Δ_k^+ represent the shortage and surplus of blood at demand point R_k, respectively.

The expected values of the shortage (Δ_k^-) and the surplus (Δ_k^+) are given by:

$$E(\Delta_k^-) = \int_{v_k}^{\infty} (t - v_k)\mathcal{F}_k(t)dt, \qquad k = 1, \ldots, n_R, \tag{3.4}$$

$$E(\Delta_k^+) = \int_0^{v_k} (v_k - t)\mathcal{F}_k(t)dt, \qquad k = 1, \ldots, n_R. \tag{3.5}$$

Due to the vitalness of the availability of blood at the demand points, a relatively large penalty of λ_k^- is associated with the shortage of a unit of blood at demand point R_k, where λ_k^- corresponds to the social cost of a death or a severe injury of a patient, due to a blood shortage. Also, since blood is extremely perishable and will be outdated if not used over a certain period after being delivered, the outdating penalty of λ_k^+ is assigned to the unit of a possible supply surplus. Note that, in the

formulation, this surplus penalty is charged to the organization even though the ARC is not directly responsible for the outdated blood at the hospitals once it is delivered to them. This is because human blood is scarce, and the ARC aims to minimize the amount of outdated blood at demand points, which actually dominates the amount of blood waste during the other activities of blood banking within the ARC network (Rios (2010)). Hence, λ_k^+, in the case of blood (as for other perishable products), includes the cost of short-term inventory holding (cold storage), and, possibly, the discarding cost of the outdated product. It is necessary to mention that having excess supplies outdated at the demand points not only imposes a discarding cost on the already financially stressed healthcare institutions such as hospitals, but also leads to further environmental damage. Similar examples of penalty costs, due to excessive supplies, as well as to shortages, can be found in the literature (see, e.g., Dong, Zhang, and Nagurney (2004) and Nagurney, Yu, and Qiang (2011)). These penalties can be assessed by the authority who is contracting with the organization to deliver the blood.

Thus, the expected total penalty at demand point $k; k = 1, \ldots, n_R$, is:

$$E(\lambda_k^- \Delta_k^- + \lambda_k^+ \Delta_k^+) = \lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+). \tag{3.6}$$

Nevertheless, the demand points (such as hospitals) are not the only modules of the blood supply chain in which the perishability of the collected blood occurs. Throughout the processes of blood collection, shipment, testing and processing, storage, and distribution, a fraction of the collected blood may deteriorate, be lost, or be wasted. The fraction of the lost product depends on the type of the activity since various processes of collection, testing, storage, etc., lead to different amounts of waste. This fraction, in general, can also be different among the various facilities at the same tier of the network, depending upon the technology used, the efficiency of the staff personnel, and so forth.

Hence, with every link a in the network, a multiplier α_a is associated, which, for all activities of the blood supply chain, lies in the range of (0,1] where $\alpha_a = 1$ means that 100% of the initial flow on link a reaches the successor node of that link, reflecting that there is no waste/loss on link a. The average percentage of loss due to the testing process was reported to be 1.7% (Sullivan et al. (2007)); consequently, the corresponding multiplier, α_a, would be equal to $1 - 0.017 = 0.983$.

As mentioned earlier, f_a denotes the (initial) flow on link a. Let f'_a denote the final flow on that link; i.e., the flow that reaches the successor node of the link. Therefore,

$$f'_a = \alpha_a f_a, \qquad \forall a \in L. \tag{3.7}$$

Thus, the waste/loss on link a is equal to:

$$f_a - f'_a = (1 - \alpha_a) f_a, \qquad \forall a \in L. \tag{3.8}$$

The organization such as ARC is responsible for discarding this waste which is potentially hazardous. Medical waste disposal contractors are typically employed to remove and dispose of the waste. Since α_a is constant, and known a priori, a total discarding cost function, $\hat{z}_a$, can be defined accordingly, which is a function of the flow, f_a, and is assumed to be convex and continuously differentiable:

$$\hat{z}_a = \hat{z}_a(f_a), \qquad \forall a \in L. \tag{3.9}$$

Let x_p represent the (initial) flow of blood (or a general perishable product) on path p joining the origin node with a destination node. The path flows must be nonnegative, that is,

$$x_p \geq 0, \qquad \forall p \in \mathcal{P}, \tag{3.10}$$

since the product will be collected, shipped, etc., in nonnegative quantities.

Let μ_p denote the multiplier corresponding to the throughput on path p, which is defined as the product of all link multipliers on links comprising that path, that is,

$$\mu_p \equiv \prod_{a \in p} \alpha_a, \qquad \forall p \in \mathcal{P}. \tag{3.11}$$

The projected demand at demand point R_k, v_k, is the sum of all the final flows on paths joining $(1, R_k)$:

$$v_k \equiv \sum_{p \in \mathcal{P}_k} x_p \mu_p, \qquad k = 1, \ldots, n_R. \tag{3.12}$$

Indeed, although the amount of blood that originates on a path p is x_p, the amount (due to perishability) that actually arrives at the destination of this path is $x_p \mu_p$.

Define, also, the multiplier, α_{ap}, which is the product of the multipliers of the links on path p that precede link a in that path. This multiplier can be expressed as:

$$\alpha_{ap} \equiv \begin{cases} \delta_{ap} \prod_{a' < a} \alpha_{a'}, & \text{if } \{a' < a\} \neq \emptyset, \\ \\ \delta_{ap}, & \text{if } \{a' < a\} = \emptyset, \end{cases} \tag{3.13}$$

where $\{a' < a\}$ denotes the set of the links preceding link a in path p, δ_{ap} is defined as equal to 1 if link a is contained in path p, and 0, otherwise, and $\emptyset$ denotes the null set. Hence, α_{ap} is equal to the product of all link multipliers preceding link a in path p. If link a is not contained in path p, then α_{ap} is set to zero. If a belongs to the first set of links, the blood collection links, this multiplier is equal to 1. The relationship between the link flow, f_a, and the path flows is as follows:

$$f_a = \sum_{p \in \mathcal{P}} x_p \, \alpha_{ap}, \qquad \forall a \in L. \tag{3.14}$$

Similar examples of multipliers corresponding to the loss/waste on links or paths can be found in the literature (see, e.g., Nagurney and Aronson (1989)).

Group the path flows into the vector x. The link flows, and the projected demands are grouped into the respective vectors f and v.

The total cost minimization objective faced by the organization includes the total cost of operating the various links, the total discarding cost of waste/loss over the links, and the expected total blood supply shortage cost as well as the total discarding cost of outdated blood at the demand points. This optimization problem can be expressed as:

$$\text{Minimize} \quad \sum_{a \in L} \hat{c}_a(f_a) + \sum_{a \in L} \hat{z}_a(f_a) + \sum_{k=1}^{n_R} \big(\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+)\big), \tag{3.15}$$

subject to: (3.10), (3.12), and (3.14).

As mentioned earlier, the minimization of total costs is not the only objective of suppliers of perishable goods. One of the most significant challenges for the ARC, for example, is to capture the risk associated with different activities in the blood supply chain network. Unlike the demand which can be projected according to the historical data, albeit with some uncertainty involved, the amount of donated blood at the collection sites has been observed to be highly stochastic.

According to Ben Natan and Gorkov (2011), most developed countries have chronic shortages of blood supply, raising questions regarding the recruiting of blood donors. As noted by Riley, Schwei, and McCullough (2007), less than 38% of the United States population is eligible to donate blood, and less than 10% of those actually donate annually. Even though the ARC encourages blood donors to make appointments beforehand, donors may miss their appointments due to inclement weather situations, traffic, personal issues, etc. (Rios (2010)). It is noted that the shortages of all blood types mostly occur during the summer and winter holidays (America's Blood Centers (2011)). Interestingly, disasters, such as the 2010 earthquake in Haiti, may stimulate people's sympathy and dramatically increase the number of blood donors.

As in Nagurney et al. (2005), I introduce a total risk function $\hat{r}_a$ corresponding to link a for every blood collection link, which denotes the variance/covariance associated with the stochasticity of blood collection. This function is assumed to be convex and continuously differentiable, and a function of the flow, that is, the amount of collected blood, on its corresponding link. The organization attempts to minimize the total risk over all links connecting the first two tiers of the network, denoted by $L_1 \subset L$. The remainder of the links in the network, i.e., the shipment of collected blood, the processing, the storage, shipment, and the distribution links, comprise the set L_1^C. The subset L_1 and its complement L_1^C partition the entire set of links L, that is, $L_1 \cup L_1^C = L$.

Thus, the risk minimization objective function for the organization can be expressed as:

$$\text{Minimize} \quad \sum_{a \in L_1} \hat{r}_a(f_a), \tag{3.16}$$

where $\hat{r}_a = \hat{r}_a(f_a)$ is the total risk function on link a.

The supply chain network optimization problem for a regionalized blood banking system can be expressed as a multicriteria decision-making problem. The organization seeks to determine the optimal levels of blood processed on each supply chain network link subject to the minimization of the total cost (operational and discarding) as well as the minimization of the total supply risk. Associate with the total supply risk objective, (3.16), a risk aversion factor θ, which is assigned by the decision-maker. Thus, the multicriteria optimization problem is:

$$\text{Minimize} \quad \sum_{a \in L} \hat{c}_a(f_a) + \sum_{a \in L} \hat{z}_a(f_a) + \sum_{k=1}^{n_R} \left(\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+)\right) + \theta \sum_{a \in L_1} \hat{r}_a(f_a), \tag{3.17}$$

subject to: (3.10), (3.12), and (3.14).

The above optimization problem is in terms of link flows. It can also be expressed in terms of path flows:

$$\text{Minimize} \quad \sum_{p\in\mathcal{P}}\big(\hat{C}_p(x)+\hat{Z}_p(x)\big)+\sum_{k=1}^{n_R}\big(\lambda_k^- E(\Delta_k^-)+\lambda_k^+ E(\Delta_k^+)\big)+\ \theta\sum_{p\in\mathcal{P}}\hat{R}_p(x), \quad (3.18)$$

subject to: (3.10) and (3.12), where the total operational cost, $\hat{C}_p(x)$, the total discarding cost, $\hat{Z}_p(x)$, and the total risk, $\hat{R}_p(x)$, corresponding to path p are, respectively, derived from $C_p(x)$, $Z_p(x)$, and $R_p(x)$ as follows:

$$\hat{C}_p(x) = x_p \times C_p(x), \qquad \forall p \in \mathcal{P}, \tag{3.19a}$$

$$\hat{Z}_p(x) = x_p \times Z_p(x), \qquad \forall p \in \mathcal{P}, \tag{3.19b}$$

$$\hat{R}_p(x) = x_p \times R_p(x), \qquad \forall p \in \mathcal{P}, \tag{3.19c}$$

with the unit cost functions on path p, i.e., $C_p(x), Z_p(x)$, and $R_p(x)$, in turn,as below:

$$C_p(x) \equiv \sum_{a\in L} c_a(f_a)\alpha_{ap}, \qquad \forall p \in \mathcal{P}, \tag{3.20a}$$

$$Z_p(x) \equiv \sum_{a\in L} z_a(f_a)\alpha_{ap}, \qquad \forall p \in \mathcal{P}, \tag{3.20b}$$

$$R_p(x) \equiv \sum_{a\in L_1} r_a(f_a)\alpha_{ap}, \qquad \forall p \in \mathcal{P}. \tag{3.20c}$$

Next, I present some preliminaries that allow the expression of the partial derivatives of the expected total shortage and discarding costs of outdated blood at the demand points solely in terms of path flow variables. Observe that, for each O/D pair $(1, R_k)$:

$$\frac{\partial E(\Delta_k^-)}{\partial x_p} = \frac{\partial E(\Delta_k^-)}{\partial v_k} \times \frac{\partial v_k}{\partial x_p}, \qquad \forall p \in \mathcal{P}_k; k = 1, \ldots, n_R. \tag{3.21}$$

By Leibniz's integral rule:

$$\frac{\partial E(\Delta_k^-)}{\partial v_k} = \frac{\partial}{\partial v_k}\left(\int_{v_k}^{\infty}(t-v_k)\mathcal{F}_k(t)dt\right) = \int_{v_k}^{\infty}\frac{\partial}{\partial v_k}(t-v_k)\mathcal{F}_k(t)dt$$

$$= P_k(v_k) - 1, \qquad k = 1, \ldots, n_R. \tag{3.22a}$$

Therefore,

$$\frac{\partial E(\Delta_k^-)}{\partial v_k} = P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right) - 1, \qquad k = 1, \ldots, n_R. \tag{3.22b}$$

On the other hand:

$$\frac{\partial v_k}{\partial x_p} = \frac{\partial}{\partial x_p}\sum_{p\in\mathcal{P}_k} x_p\mu_p = \mu_p, \qquad \forall p \in \mathcal{P}_k; k = 1, \ldots, n_R. \tag{3.23}$$

The above is correct since the μ_ps are constant values. Therefore, from (3.22b) and (3.23), the following conclusion holds:

$$\frac{\partial E(\Delta_k^-)}{\partial x_p} = \mu_p\left[P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right) - 1\right], \qquad \forall p \in \mathcal{P}_k; k = 1, \ldots, n_R. \tag{3.24}$$

Similarly, for the surplus:

$$\frac{\partial E(\Delta_k^+)}{\partial x_p} = \frac{\partial E(\Delta_k^+)}{\partial v_k} \times \frac{\partial v_k}{\partial x_p}, \qquad \forall p \in \mathcal{P}_k; k = 1, \ldots, n_R, \tag{3.25}$$

$$\frac{\partial E(\Delta_k^+)}{\partial v_k} = \frac{\partial}{\partial v_k}\left(\int_0^{v_k}(v_k-t)\mathcal{F}_k(t)dt\right) = \int_0^{v_k}\frac{\partial}{\partial v_k}(v_k-t)\mathcal{F}_k(t)dt$$

$$= P_k(v_k), \qquad k = 1, \ldots, n_R. \tag{3.26a}$$

Thus,

$$\frac{\partial E(\Delta_k^+)}{\partial v_k} = P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right), \qquad k = 1, \ldots, n_R. \tag{3.26b}$$

From (3.26b) and (3.23):

$$\frac{\partial E(\Delta_k^+)}{\partial x_p} = \mu_p P_k \left(\sum_{p \in \mathcal{P}_k} x_p \mu_p \right), \qquad \forall p \in \mathcal{P}_k; k = 1, \ldots, n_R. \tag{3.27}$$

Let K denote the feasible set such that:

$$K \equiv \{x | x \in R_+^{n_\mathcal{P}}\}. \tag{3.28}$$

Before deriving the variational inequality formulation of the problem, I establish a lemma that formalizes the construction of the partial derivatives of the path total operational cost, the total discarding cost, and the total risk with respect to a path flow.

Lemma 3.1

The partial derivatives of the total operational cost, the total discarding cost, and the total risk with respect to the corresponding path flow are, respectively, given by:

$$\frac{\partial (\sum_{q \in \mathcal{P}} \hat{C}_q(x))}{\partial x_p} = \sum_{a \in L} \frac{\partial \hat{c}_a(f_a)}{\partial f_a} \alpha_{ap}, \quad \forall p \in \mathcal{P}, \tag{3.29a}$$

$$\frac{\partial (\sum_{q \in \mathcal{P}} \hat{Z}_q(x))}{\partial x_p} = \sum_{a \in L} \frac{\partial \hat{z}_a(f_a)}{\partial f_a} \alpha_{ap}, \quad \forall p \in \mathcal{P}, \tag{3.29b}$$

$$\frac{\partial (\sum_{q \in \mathcal{P}} \hat{R}_q(x))}{\partial x_p} = \sum_{a \in L_1} \frac{\partial \hat{r}_a(f_a)}{\partial f_a} \alpha_{ap}, \quad \forall p \in \mathcal{P}. \tag{3.29c}$$

Proof: I establish the equivalence for (3.29a); the equivalences (3.29b) and (3.29c) can be obtained in a similar fashion. The partial derivative of the total operational cost with respect to the flow on path p is:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q)}{\partial x_p} = \sum_{q\in\mathcal{P}} \frac{\partial \hat{C}_q}{\partial x_p}, \qquad \forall p \in \mathcal{P}, \tag{3.30a}$$

which, based on the total path cost (3.19a), can be rewritten as:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q)}{\partial x_p} = \sum_{q\in\mathcal{P}} \frac{\partial(C_q x_q)}{\partial x_p} = C_p + \sum_{q\in\mathcal{P}} x_q \frac{\partial C_q}{\partial x_p}, \qquad \forall p \in \mathcal{P}. \tag{3.30b}$$

According to the definition of $C_q(x)$ in (3.20a):

$$\frac{\partial C_q}{\partial x_p} = \frac{\partial(\sum_{a\in L} c_a \alpha_{aq})}{\partial x_p} = \sum_{a\in L} \frac{\partial c_a}{\partial x_p}\alpha_{aq} = \sum_{a\in L} \frac{\partial c_a}{\partial f_a}\frac{\partial f_a}{\partial x_p}\alpha_{aq}, \quad \forall p, q \in \mathcal{P}. \tag{3.31}$$

On the other hand, by referring to (3.14), yields:

$$\frac{\partial f_a}{\partial x_p} = \alpha_{ap}, \qquad \forall a \in L, \forall p \in \mathcal{P}. \tag{3.32}$$

From (3.31) and (3.32), one obtains:

$$\frac{\partial C_q}{\partial x_p} = \sum_{a\in L} \frac{\partial c_a}{\partial f_a}\alpha_{ap}\alpha_{aq}, \qquad \forall p, q \in \mathcal{P}. \tag{3.33}$$

Substituting (3.33) into (3.30b) yields:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q)}{\partial x_p} = C_p + \sum_{q\in\mathcal{P}} x_q \sum_{a\in L} \frac{\partial c_a}{\partial f_a}\alpha_{ap}\alpha_{aq} = C_p + \sum_{a\in L}\sum_{q\in\mathcal{P}} x_q \frac{\partial c_a}{\partial f_a}\alpha_{ap}\alpha_{aq}. \tag{3.34}$$

Thus,

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q)}{\partial x_p} = C_p + \sum_{a\in L}\frac{\partial c_a}{\partial f_a}\alpha_{ap}\sum_{q\in\mathcal{P}}x_q\alpha_{aq}, \qquad \forall p\in\mathcal{P}. \tag{3.35}$$

By substituting proper equivalences from (3.14) and (3.20a) into (3.35), one gets:

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q)}{\partial x_p} = \sum_{a\in L}c_a\alpha_{ap} + \sum_{a\in L}\frac{\partial c_a}{\partial f_a}\alpha_{ap}f_a = \sum_{a\in L}(c_a + \frac{\partial c_a}{\partial f_a}f_a)\alpha_{ap}, \qquad \forall p\in\mathcal{P}. \tag{3.36}$$

On the other hand, from (3.1):

$$\frac{\partial \hat{c}_a}{\partial f_a} = c_a + \frac{\partial c_a}{\partial f_a}f_a, \qquad \forall a\in L. \tag{3.37}$$

From (3.36) and (3.37), one concludes that

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q)}{\partial x_p} = \sum_{a\in L}\frac{\partial \hat{c}_a(f_a)}{\partial f_a}\alpha_{ap}, \qquad \forall p\in\mathcal{P}. \tag{3.38}$$

Thus, (3.29a) has been established. □

I now derive the variational inequality formulation of the blood supply chain network optimization problem in terms of path flows and link flows.

Theorem 3.1

The vector x^* is an optimal solution to the multicriteria optimization problem (3.18), subject to (3.10) and (3.12), if and only if it is a solution to the variational inequality problem: determine the vector of optimal path flows $x^*\in K$, such that:

$$\sum_{k=1}^{n_R}\sum_{p\in\mathcal{P}_k}\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_p}+\frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_p}+\lambda_k^+\mu_p P_k\left(\sum_{p\in\mathcal{P}_k}x_p^*\mu_p\right)\right.$$

$$\left.-\lambda_k^-\mu_p\left(1-P_k\left(\sum_{p\in\mathcal{P}_k}x_p^*\mu_p\right)\right)+\theta\ \frac{\partial(\sum_{q\in\mathcal{P}}\hat{R}_q(x^*))}{\partial x_p}\right]\times[x_p-x_p^*]\geq 0,\qquad \forall x\in K. \tag{3.39}$$

The variational inequality (3.39), in turn, can be rewritten in terms of link flows as: determine the vector of optimal link flows, and the vector of optimal projected demands $(f^*, v^*)\in K^1$, *such that:*

$$\sum_{a\in L_1}\left[\frac{\partial\hat{c}_a(f_a^*)}{\partial f_a}+\frac{\partial\hat{z}_a(f_a^*)}{\partial f_a}+\theta\ \frac{\partial\hat{r}_a(f_a^*)}{\partial f_a}\right]\times[f_a-f_a^*]+\sum_{a\in L_1^C}\left[\frac{\partial\hat{c}_a(f_a^*)}{\partial f_a}+\frac{\partial\hat{z}_a(f_a^*)}{\partial f_a}\right]\times[f_a-f_a^*]$$

$$+\sum_{k=1}^{n_R}\left[\lambda_k^+P_k(v_k^*)-\lambda_k^-(1-P_k(v_k^*))\right]\times[v_k-v_k^*]\geq 0,\qquad \forall(f,v)\in K^1, \tag{3.40}$$

where K^1 *denotes the feasible set as defined below:*

$$K^1\equiv\{(f,v)|\exists x\geq 0,\ (3.12)\ \textit{and}\ (3.14)\ \textit{hold}\}. \tag{3.41}$$

Proof: First, I prove the result for path flows (cf. (3.39)).

The convexity of $\hat{C}_p$, $\hat{Z}_p$, and $\hat{R}_p$ for all paths p holds since $\hat{c}_a$, $\hat{z}_a$, and $\hat{r}_a$ were assumed to be convex for all links a, and θ is nonnegative. I need to verify that $\lambda_k^-E(\Delta_k^-)+\lambda_k^+E(\Delta_k^+)$ is also convex. Note that

$$\frac{\partial^2}{\partial {x_p}^2}\left[\lambda_k^-E(\Delta_k^-)+\lambda_k^+E(\Delta_k^+)\right]=\lambda_k^-\ \frac{\partial^2E(\Delta_k^-)}{\partial {x_p}^2}+\lambda_k^+\ \frac{\partial^2E(\Delta_k^+)}{\partial {x_p}^2},$$

$$\forall p\in\mathcal{P}_k; k=1,\ldots,n_R. \tag{3.42a}$$

Substituting the first order derivatives from (3.24) and (3.27) into (3.42a) yields:

$$\frac{\partial^2}{\partial {x_p}^2}\left[\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+)\right]$$

$$= \lambda_k^- \frac{\partial}{\partial x_p}\mu_p \left[P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right) - 1\right] + \lambda_k^+ \frac{\partial}{\partial x_p}\mu_p P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right)$$

$$= (\lambda_k^- + \lambda_k^+)(\mu_p)^2 \mathcal{F}_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right) > 0, \qquad \forall p \in \mathcal{P}_k; k = 1,\ldots,n_R. \tag{3.42b}$$

The above inequality holds provided that $(\lambda_k^- + \lambda_k^+)$, i.e., the sum of shortage and surplus penalties, is assumed to be positive. Hence, $\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+)$, and, as a consequence, the multicriteria objective function in (3.18) is also convex.

Since the objective function (3.18) is convex and the feasible set K is closed and convex, the variational inequality (3.39) follows from the standard theory of variational inequalities (see Nagurney (1999)).

As for the proof of the variational inequality (3.40), now that (3.39) is established, one can apply Lemma 3.1. Also, from (3.12) and (3.14), one can rewrite the formulation in terms of link flows and projected demands rather than path flows. Thus, the second part of Theorem 3.1, that is, the variational inequality in link flows (3.40), holds. □

Note that variational inequality (3.39) can be put into standard form (cf. (2.1)) as follows: determine $X^* \in \mathcal{K}$ such that:

$$\langle F(X^*)^T, X - X^*\rangle \geq 0, \qquad \forall X \in \mathcal{K}. \tag{3.43}$$

Define the feasible set $\mathcal{K} \equiv K$, the vector $X \equiv x$, and $F(X)$, such that:

$$F(X) \equiv \left[\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x))}{\partial x_p} + \frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x))}{\partial x_p} + \lambda_k^+ \mu_p P_k\left(\sum_{p\in\mathcal{P}_k} x_p\mu_p\right)\right.$$

$$-\lambda_k^- \mu_p \left(1 - P_k \left(\sum_{p \in \mathcal{P}_k} x_p \mu_p\right)\right) + \theta \frac{\partial(\sum_{q \in \mathcal{P}} \hat{R}_q(x))}{\partial x_p}; \quad p \in \mathcal{P}_k; k = 1, \ldots, n_R \Bigg], \quad (3.44)$$

then the variational inequality (3.39) can be reexpressed in standard form (3.43).

I utilize variational inequality (3.39) in path flows for the purpose of computations since the proposed computational procedure yields closed form expressions at each iteration. Once problem (3.39) is solved, by using (3.14), which relates the links flows to the path flows, one can obtain the solution f^* that minimizes the total cost as well as the total supply risk (cf. (3.17)) associated with the optimization of the supply chain network of a regionalized blood banking system.

3.2. Illustrative Blood Supply Chain Network Numerical Examples

In order to further illustrate the above model, I now present several examples. Consider the blood supply chain network topology in Figure 3.2 in which the organization has a single blood collection site, a single blood center, one component lab, one storage facility, a single distribution center and is to serve a single demand point. The links are labeled a, b, c, d, e, and f.

3.2.1 Example 3.1

The total cost functions on the links were:

$$\hat{c}_a(f_a) = f_a^2 + 6f_a, \quad \hat{c}_b(f_b) = 2f_b^2 + 7f_b, \quad \hat{c}_c(f_c) = f_c^2 + 11f_c, \quad \hat{c}_d(f_d) = 3f_d^2 + 11f_d,$$
$$\hat{c}_e(f_e) = f_e^2 + 2f_e, \quad \hat{c}_f(f_f) = f_f^2 + f_f.$$

I assumed that there was no waste so that $\alpha_a = 1$ for all links in Figure 3.2. Hence, all the functions $\hat{z}_a$ were set equal to 0 for all the links $a, \ldots, f$.

The total risk cost function on the blood collection link a was: $\hat{r}_a = 2f_a^2$, and the risk aversion factor, θ, was assumed to be 1.

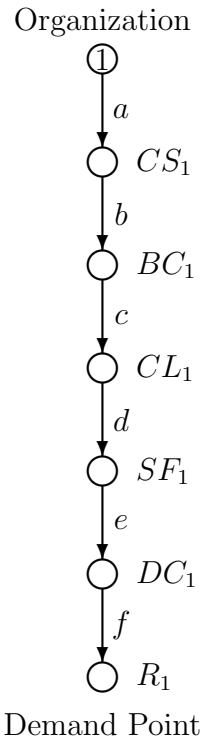

Figure 3.2. Supply Chain Network Topology for Numerical Examples 3.1 and 3.2

There is only a single path p_1 which was defined as: $p_1 = (a, b, c, d, e, f)$ with $\mu_{p_1} = 1$.

I assumed that the demand for the product followed a uniform distribution on the interval $[0, 5]$ so that $P_1(x_{p_1}) = \frac{x_{p_1}}{5}$. The penalties were: $\lambda_1^- = 100, \quad \lambda_1^+ = 0$.

Substitution of the values of $\lambda_1^+, \lambda_1^-, \mu_{p_1}$, and θ into (3.39), yields:

$$\left[\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x^*))}{\partial x_{p_1}} - 100(1 - P_1(x^*_{p_1})) + \frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x^*))}{\partial x_{p_1}}\right] \times [x_{p_1} - x^*_{p_1}] \geq 0, \qquad \forall x \in K. \tag{3.45}$$

Under the assumption that $x^*_{p_1} > 0$, the left-hand side of inequality (3.45) must be equal to zero, that is:

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_1}} - 100(1 - P_1(x^*_{p_1})) + \frac{\partial(\sum_{q\in\mathcal{P}}\hat{R}_q(x^*))}{\partial x_{p_1}} = 0. \tag{3.46}$$

It follows from Lemma 3.1 that

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_1}} = \frac{\partial\hat{c}_a(f^*_a)}{\partial f_a}\alpha_{ap_1} + \frac{\partial\hat{c}_b(f^*_b)}{\partial f_b}\alpha_{bp_1} + \frac{\partial\hat{c}_c(f^*_c)}{\partial f_c}\alpha_{cp_1}$$

$$+\frac{\partial\hat{c}_d(f^*_d)}{\partial f_d}\alpha_{dp_1} + \frac{\partial\hat{c}_e(f^*_e)}{\partial f_e}\alpha_{ep_1} + \frac{\partial\hat{c}_f(f^*_f)}{\partial f_f}\alpha_{fp_1}. \tag{3.47}$$

Since $\alpha_{ap_1} = \alpha_{bp_1} = \alpha_{cp_1} = \alpha_{dp_1} = \alpha_{ep_1} = \alpha_{fp_1} = 1$, and $f^*_a = f^*_b = f^*_c = f^*_d = f^*_e = f^*_f = x^*_{p_1}$, with substitution into (3.47), yields:

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_1}} = (2f^*_a+6)+(4f^*_b+7)+(2f^*_c+11)+(6f^*_d+11)+(2f^*_e+2)+(2f^*_f+1)$$

$$= 18x^*_{p_1} + 38. \tag{3.48}$$

Similarly:

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{R}_q(x^*))}{\partial x_{p_1}} = \frac{\partial\hat{r}_a(f^*_a)}{\partial f_a}\alpha_{ap_1} = 4f^*_a = 4x^*_{p_1}. \tag{3.49}$$

Therefore, using the above relationships, (3.46) may be reexpressed as:

$$18x^*_{p_1} + 38 - 100(1 - \frac{x^*_{p_1}}{5}) + 4x^*_{p_1} = 0, \tag{3.50}$$

whose solution yields the optimal path flow: $x^*_{p_1}$= 1.48, and the corresponding optimal link flow pattern: $f^*_a = f^*_b = f^*_c = f^*_d = f^*_e = f^*_f = 1.48$. Following (3.12), the projected demand is equal to: $v^*_1 = x^*_{p_1} = 1.48$.

3.2.2 Example 3.2

Example 3.2 had the same data as Example 3.1 except that now there was a loss associated with the testing and processing link with $\alpha_c = .8$. Hence, I now set (cf. (3.9)) $\hat{z}_c = .5f_c^2$ and $\mu_{p_1} = \alpha_c = .8$.

Similar to the solution procedure used for Example 3.1, from variational inequality formulation (3.39), under the assumption that $x^*_{p_1} > 0$, the following equation must hold for Example 3.2:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x^*))}{\partial x_{p_1}} + \frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x^*))}{\partial x_{p_1}} - 100 \times 0.8(1 - P_1(0.8 \times x^*_{p_1})) + \frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x^*))}{\partial x_{p_1}} = 0. \tag{3.51}$$

Since in this example, $\alpha_{ap_1} = \alpha_{bp_1} = \alpha_{cp_1} = 1$, $\alpha_{dp_1} = \alpha_{ep_1} = \alpha_{fp_1} = 0.8$, $f^*_a = f^*_b = f^*_c = x^*_{p_1}$, and $f^*_d = f^*_e = f^*_f = 0.8x^*_{p_1}$, therefore:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x^*))}{\partial x_{p_1}} =$$

$$(2f^*_a + 6) + (4f^*_b + 7) + (2f^*_c + 11) + 0.8(6f^*_d + 11) + 0.8(2f^*_e + 2) + 0.8(2f^*_f + 1) =$$

$$8x^*_{p_1} + 24 + 0.8(10 \times 0.8x^*_{p_1} + 14) = 14.4x^*_{p_1} + 35.2. \tag{3.52}$$

Also,

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x^*))}{\partial x_{p_1}} = \frac{\partial \hat{z}_c(f^*_c)}{\partial f_c}\alpha_{cp_1} = f^*_c = x^*_{p_1}. \tag{3.53}$$

The partial derivative of the total risk function was equal to that of Example 3.1:

$$\frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x^*))}{\partial x_{p_1}} = \frac{\partial \hat{r}_a(f^*_a)}{\partial f_a}\alpha_{ap_1} = 4f^*_a = 4x^*_{p_1}. \tag{3.54}$$

However, now:

$$P_1(0.8x^*_{p_1}) = \frac{0.8x^*_{p_1}}{5}. \tag{3.55}$$

Therefore, the following equation needs to be solved:

$$14.4x^*_{p_1} + 35.2 + x^*_{p_1} - 80(1 - \frac{0.8x^*_{p_1}}{5}) + 4x^*_{p_1} = 0. \tag{3.56}$$

The new optimal path flow solution is: $x^*_{p_1} = 1.39$, which corresponds to the optimal link flow pattern: $f^*_a = f^*_b = f^*_c = 1.39$, and $f^*_d = f^*_e = f^*_f = 1.11$. The projected demand is: $v^*_1 = x^*_{p_1}\mu_{p_1} = 1.11$. Comparing the results of Examples 3.1 and 3.2 reveals the fact that when perishability is taken into consideration, with $\alpha_c = .8$ and the above data, the organization chooses to produce/ship slightly smaller quantities so as to minimize the discarding cost of the waste, despite the shortage penalty of λ^-_1.

Note that when $\lambda^-_1 = 200$, the optimal path flow solution becomes: $x^*_{p_1} = 2.77$, and the corresponding optimal link flow pattern: $f^*_a = f^*_b = f^*_c = 2.77$, and $f^*_d = f^*_e = f^*_f = 2.22$, with a projected demand of: $v^*_1 = x^*_{p_1}\mu_{p_1} = 2.22$.

In fact, using equation (3.51), with λ^-_1 substituted for 100, one can derive the optimal path flow $x^*_{p_1}$ as a function of λ^-_1, that is:

$$x^*_{p_1} = \frac{100(\lambda^-_1 - 44)}{16\lambda^-_1 + 2425}. \tag{3.57}$$

Therefore, an appropriate increase in the unit shortage penalty cost λ^-_1 results in the organization processing larger volumes of the blood product, even exceeding the optimal flow in Example 3.1, which makes sense intuitively. Furthermore. for $\lambda^-_1 \leq 44$, the organization acquires and, hence, processes and distributes, zero units of the blood product.

Table 3.1. Computed Optimal Path Flows $x^*_{p_1}$ and Optimal Values of the Objective Function in Example 3.2 as α_c and λ_1^- Vary

λ_1^- \ α_c		.2	.4	.6	.8	1
100	$x^*_{p_1}$	0.00	0.58	1.16	1.39	1.48
	OF	250.00	246.96	234.00	218.83	204.24
200	$x^*_{p_1}$	0.88	2.40	2.83	2.77	2.61
	OF	494.19	439.52	376.23	326.94	288.35
300	$x^*_{p_1}$	2.10	3.74	3.86	3.54	3.20
	OF	715.12	581.15	464.85	387.17	331.44
400	$x^*_{p_1}$	3.20	4.76	4.57	4.03	3.55
	OF	914.75	689.71	525.36	425.56	357.63
500	$x^*_{p_1}$	4.20	5.57	5.09	4.37	3.79
	OF	1096.03	775.55	569.30	452.16	375.23
1000	$x^*_{p_1}$	8.09	7.95	6.41	5.19	4.33
	OF	1799.11	1027.94	681.89	515.88	415.67
2000	$x^*_{p_1}$	12.69	9.80	7.27	5.68	4.65
	OF	2631.32	1224.45	755.64	554.47	439.05
3000	$x^*_{p_1}$	15.33	10.58	7.60	5.86	4.76
	OF	3107.51	1307.25	783.73	568.57	447.39
4000	$x^*_{p_1}$	17.03	11.01	7.77	5.96	4.82
	OF	3415.88	1352.89	798.54	575.88	451.68

3.2.3 Sensitivity Analysis

I conducted additional sensitivity analysis by varying the loss associated with the testing and processing activity, α_c, and the unit shortage penalty cost, λ_1^-, respectively. The computed optimal path flows $x^*_{p_1}$ and the optimal values of the objective function (OF) (3.18) are reported in Table 3.1.

It is interesting to note from Table 3.1 that, under a specific unit penalty cost, the path flow will be reduced when the loss of testing and processing, $(1 - \alpha_c)$, increases within some specific range. For instance, when λ_1^- is 200 and the loss, $1-\alpha_c$, increases from 0.4 to 0.8, the optimal path flow decreases from 2.83 to 0.88. However, the optimal value of the objective function always keeps on increasing. Table 3.1 also illustrates, under the same loss associated with testing and processing, the optimal path flow rises with an increase in the unit shortage penalty cost, λ_1^-.

The optimal path flow in Example 3.2, assuming a nonnegative value, as a function of the link multiplier and the shortage penalty *simultaneously* can be expressed as follows:

$$x^*_{p_1} = \frac{5\alpha_c(\lambda_1^- - 14) - 120}{\alpha_c^2(\lambda_1^- + 50) + 65}. \tag{3.58}$$

3.3. The Algorithm and an Additional Numerical Example

In this section, I utilize the Euler method – presented in Section 2.6 – to find the optimal solution to larger-scale blood banking problems. Realization of the Euler method for the solution of the blood bank supply chain management problem governed by variational inequality (3.39) (see also (3.43)) induces subproblems that can be solved explicitly and in closed form (Dupuis and Nagurney (1993) and Nagurney and Zhang (1996)).

Explicit Formulae for the Euler Method Applied to the Blood Supply Chain Network Variational Inequality (3.39)

The elegance of this procedure for the computation of solutions to the blood supply chain network operations management problem modeled in Section 3.2 can be seen in the following explicit formulae. In particular, (2.47) for the blood supply chain network management problem governed by variational inequality problem (3.39) yields the following closed form expression for the blood product path flow on each path at iteration $\tau + 1$:

$$x_p^{\tau+1} = \max\{0, x_p^\tau + a_\tau(\lambda_k^- \mu_p(1 - P_k(\sum_{p\in\mathcal{P}_k} x_p^\tau \mu_p)) - \lambda_k^+ \mu_p P_k(\sum_{p\in\mathcal{P}_k} x_p^\tau \mu_p)$$

$$- \frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x^\tau))}{\partial x_p} - \frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x^\tau))}{\partial x_p} - \theta \frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x^\tau))}{\partial x_p})\}, \qquad \forall p \in \mathcal{P}. \tag{3.59}$$

This closed form expression was applied to calculate the updated product flow during the steps of the Euler Method for the blood supply chain problem.

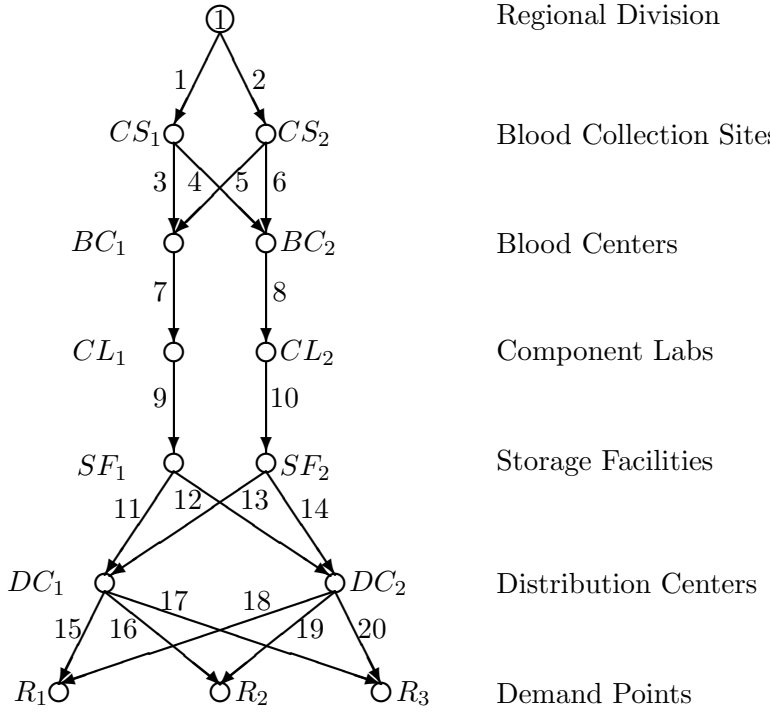

Figure 3.3. Supply Chain Network Topology for Numerical Example 3.3

3.3.1 Example 3.3

I now present a larger-scale numerical blood supply chain network problem and utilize the explicit formulae in (3.59) for its solution. The numerical example consisted of two blood collection sites, two blood centers, two component labs, two storage facilities, two distribution centers, and three demand points, as depicted in Figure 3.3.

R_1 was a small surgical center while R_2 and R_3 were larger hospitals with higher demand for red blood cells. Assuming a weekly schedule for the distribution of product to these demand points, the demands at R_1, R_2 and R_3, over the planning horizon of one week, followed a uniform probability distribution on the intervals [5,10], [40,50], and [25,40], respectively. Hence,

$$P_1(\sum_{p\in\mathcal{P}_1}\mu_p x_p) = \frac{\sum_{p\in\mathcal{P}_1}\mu_p x_p - 5}{5},\ P_2(\sum_{p\in\mathcal{P}_2}\mu_p x_p) = \frac{\sum_{p\in\mathcal{P}_2}\mu_p x_p - 40}{10},$$

$$P_3(\sum_{p\in\mathcal{P}_3}\mu_p x_p) = \frac{\sum_{p\in\mathcal{P}_3}\mu_p x_p - 25}{15},$$

where the first O/D pair of nodes is $(1, R_1)$, the second is $(1, R_2)$, and the third is $(1, R_3)$.

The shortage and outdating penalties for each of the three demand points were:

$$\lambda_1^- = 2200, \quad \lambda_1^+ = 50,$$
$$\lambda_2^- = 3000, \quad \lambda_2^+ = 60,$$
$$\lambda_3^- = 3000, \quad \lambda_3^+ = 50.$$

The total risk functions corresponding to the blood collection links were:

$$\hat{r}_1(f_1) = 2f_1^2, \quad \text{and} \quad \hat{r}_2(f_2) = 1.5f_2^2,$$

and the risk aversion factor, θ, was 0.7.

The multipliers corresponding to the links, the total cost functions, and the total discarding cost functions were as reported in Table 3.2. These numbers have been selected based on the average historical data for the American Red Cross Northeast Division Blood Services (Rios (2010)).

The Euler method (cf. (3.59)) for the solution of variational inequality (3.39) was implemented in Matlab. A Microsoft Windows System with a Dell PC at the University of Massachusetts Amherst was used for all the computations. I set the sequence $a_\tau = .1(1, \frac{1}{2}, \frac{1}{2}, \cdots)$, and the convergence tolerance was $\epsilon = 10^{-6}$, that is, the absolute value of the difference between each path flow in two successive iterations was less than or equal to this ϵ. The algorithm was initialized by setting the projected demand at each demand point and all other variables equal to zero. Table 3.2 also provides the computed optimal solutions.

Table 3.2. Total Cost and Total Discarding Cost Functions and Solution for Numerical Example 3.3

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	f_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	54.72
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	43.90
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	30.13
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	22.42
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	19.57
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	23.46
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	49.39
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	42.00
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	43.63
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	39.51
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	29.68
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	13.08
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	26.20
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	13.31
15	1.00	$1.3f_{15}^2 + 3f_{15}$	$.7f_{15}^2$	5.78
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	25.78
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	24.32
18	1.00	$.7f_{18}^2 + 2f_{18}$	$.7f_{18}^2$	.29
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	18.28
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	7.29

Thus, under the given demand probability distributions for the three demand points, the amounts of optimal product flow on each link were as reported above. These numbers clearly demonstrate the effect of the waste throughout the network, and are subject to the mentioned link multipliers as well as the various costs associated with those links, as formerly stated.

The computed amounts of projected demand for each of the three demand points were:

$$v_1^* = 6.06, \quad v_2^* = 44.05, \quad \text{and} \quad v_3^* = 30.99.$$

Note that the organization needs to procure an amount $f_1^* + f_2^* = 98.62$ with a projected demand of $v_1^* + v_2^* + v_3^* = 81.10$. Because of the product perishability, a higher amount needs to be procured than is projected on the demand side. Hence, the

model can assist decision-makers in matching supply with demand under uncertainty and product perishability.

The values of the total operational cost, the total discarding cost, and the weighted total risk at the optimal computed solution were: $55,445.55$, $11,199.90$, and $6,214.72$, respectively. The values of the total expected shortage and the total surplus penalties over the three demand points were $16,839.53$ and 114.66, respectively. As a result, the value of the objective function (3.17), equivalently, (3.18), at the optimal computed solution, was $89,814.36$.

It is interesting to note that, between the two blood collection links, although link 1 has a higher waste/loss rate, and higher total risk and discarding costs, it has a higher optimal flow of blood product as compared to link 2 due to its lower total cost function. Furthermore, for the small surgical center, R_1, the value of projected demand, $v_1^* = 6.06$, is closer to the lower bound of its uniform probability distribution due to the relatively smaller shortage penalty cost. In contrast, the values of projected demand for the larger hospitals, R_2 and R_3, are closer to the respective upper bounds of their uniform distributions.

3.4. Summary and Conclusions

In this chapter, I developed a supply chain network optimization model for the management of the procurement, testing and processing, and distribution of a perishable product – that of human blood.

The original contributions in this chapter, include the blood supply chain network model operations management model, which has the notable features that it captures perishability of this life-saving product through the use of arc multipliers; it contains discarding costs associated with waste/disposal; it handles uncertainty associated with demand points; it assesses costs associated with shortages/surpluses

at the demand points, and it also quantifies the supply-side risk associated with procurement.

For the sake of generality, and the establishment of the foundations that enable further extensions and applications, I used a variational inequality approach for model formulation and solution. I illustrated the model through transparent numerical examples, which vividly demonstrate the flexibility and generality of the presented supply chain network optimization model.

CHAPTER 4

SUPPLY CHAIN NETWORK DESIGN OF A SUSTAINABLE BLOOD BANKING SYSTEM

In Chapter 3, a supply chain network model of a perishable product with application to the operations management of a regionalized blood banking system was presented. In this chapter I study another aspect of such systems; that of the network design/redesign problem. Specifically, I consider the optimal design (or redesign) of a blood supply chain consisting of collection sites, blood centers, testing and processing labs, storage facilities, distribution centers as well as demand points. The multicriteria system-optimization approach to networks with arc multipliers captures several critical concerns associated with blood banking systems including but not limited to the determination of the optimal capacities and the optimal allocations, the induced supply-side risk, and the induced cost of discarding potentially hazardous blood waste, while the uncertain demand for blood is satisfied as closely as possible.

This chapter is based on Nagurney and Masoumi (2012) and is an extension to the operations management model developed in Chapter 3. The organization of this chapter is as follows. In Section 4.1, I develop the blood supply chain network design model that allows for the design of such a network from scratch or the redesign of an existing network. In Section 4.2, I propose the algorithmic scheme that yields closed form expressions at each iteration in terms of the product path flows, the link capacities, and the associated Lagrange multipliers. I then apply the algorithm to a spectrum of numerical examples, which illustrate the generality and applicability of the methodological and computational framework. A summary and the conclusions are provided in Section 4.3.

4.1. The Sustainable Blood Banking System Supply Chain Network Design Model

In this section, I develop the supply chain network design/redesign model for a blood banking system. As mentioned earlier, the American Red Cross shut down two of its seven testing labs over the past few years in order to reduce the overall costs of its blood services. The model presented here enables the reevaluation of such modifications to a blood supply chain network system.

For continuity purposes, the notation for the model presented in this chapter follows closely that of Chapter 3. Also, please refer to Chapter 3 for the description of various components of blood supply chain networks, and recall the network topology of a regionalized blood banking supply chain model in Figure 3.1. Assume that, in the initial supply chain network topology, as in Figure 3.1, which serves as a template upon which the optimal supply chain network design is constructed, there exists at least one path joining node 1 with each destination node. This assumption guarantees that the demand at each demand point will be met as closely as possible, given that uncertain demand for blood at each demand point is considered. The solution of the model yields the optimal investments associated with the various links as well as the optimal flows, at minimum total cost and risk, as is demonstrated and, hence, the optimal sustainable supply chain network design. The model is sufficiently flexible in that it is capable of handling either the design of the sustainable network from scratch or the redesign of an existing blood banking supply chain network since certain existing link capacities can be either enhanced or reduced.

Note that, in Figure 3.1, the top-tiered node always exists since it represents the organization. Similarly, the bottom-tiered nodes, which correspond to the demand points (such as hospitals and surgical medical centers) also always exist. The solution to this model determines if any of the links should be removed since the optimal

solution will yield zero capacities for such links or whether the capacities on links should be increased.

The possible supply chain network topology, as depicted in Figure 3.1, is represented by $G = [N, L]$, where N and L denote the sets of nodes and links, respectively. The ultimate solution of the complete model will yield the optimal capacity modifications on the various links of the network as well as the optimal flows.

The formalism that I utilize in this chapter – similar to that of Chapter 3 – is multicriteria system-optimization, where the organization wishes to determine at what level the blood collection sites should operate; the same for the blood centers, the component labs, the storage facilities, and the distribution centers. Furthermore, the organization seeks to minimize the total supply-side risk as well as the total costs associated with its blood collection, shipment, processing, storage, and distribution activities, along with the total investment corresponding to the enhancement of link capacities (or their construction from scratch), or the total induced cost of reducing link capacities, as well as the total cost of discarding the waste/perished product over the links. The demands must be satisfied as closely as possible with associated shortage penalties if the demands are not met, in addition to the outdating (surplus) penalties in the case that the organization delivers excess supply to the demand points.

The definitions of the total operational cost functions, the total discarding cost of waste, the expected shortage and surplus penalties, the arc and path multipliers, and the relationships between the link flows, path flows, and the projected demands are identical to those already presented in Chapter 3, and will not be repeated here. Formulas (3.1) to (3.14) also govern the operations aspect of the sustainable blood banking design problem, and should be considered in the design/redesign model.

In this chapter, the blood supply chain organization is assumed to not only be willing to determine which facilities should operate and at what level, but also is

interested in possibly modifying the existing capacities with the demand being satisfied as closely as possible, and the total cost and risk being minimized. Let $\bar{u}_a$ denote the nonnegative existing capacity on link $a, \forall a \in L$. The organization can enhance/reduce the capacity of link a by $u_a, \forall a \in L$. The total investment cost of adding capacity u_a on link a, or contrarily, the induced cost of lowering the capacity by u_a, is denoted by $\hat{\pi}_a$, and is a function of the change in capacity:

$$\hat{\pi}_a = \hat{\pi}_a(u_a), \qquad \forall a \in L. \tag{4.1}$$

The total capacity investment cost functions can be interpreted as the cost of purchasing/renting additional equipments, hiring extra staff personnel, and expanding the transportation fleet. On the other hand, the total cost corresponding to capacity reduction typically includes the relocation of equipment, the reallocation of personnel as well as the storing of surplus equipment. These functions are assumed to be convex and continuously differentiable. Group the link capacity changes into the vector u. Similarly, the path flows, the link flows, and the projected demands are grouped into the respective vectors x, f, and v.

The total cost minimization objective faced by the organization includes the total cost of operating the various links, the total discarding cost of waste/loss over the links, the total cost of capacity modification, and the expected total blood supply shortage cost as well as the total discarding cost of outdated blood at the demand points. This optimization problem can be expressed as:

$$\text{Minimize} \quad \sum_{a \in L} \hat{c}_a(f_a) + \sum_{a \in L} \hat{z}_a(f_a) + \sum_{a \in L} \hat{\pi}_a(u_a) + \sum_{k=1}^{n_R} \left(\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+) \right) \tag{4.2}$$

subject to: (3.10), (3.12) and (3.14), and

$$f_a \leq \bar{u}_a + u_a, \qquad \forall a \in L, \tag{4.3}$$

$$-\bar{u}_a \leq u_a, \qquad \forall a \in L. \tag{4.4}$$

Constraint (4.3) guarantees that the flow on a link cannot exceed the new capacity on that link. Furthermore, the change in link capacities can take on positive/negative values corresponding to the enhancement/reduction of the capacities. Constraint (4.4) guarantees that the flow on a link will not be negative by imposing a lower bound for this link capacity change (see Nagurney (2010b)).

Observe that if $\bar{u}_a = 0,\ \forall a \in L$, then the redesign model converts to a "design from scratch" model in that there will be no capacities on the link apriori (See Nagurney and Nagurney (2010)). Both models of redesign and design are consistent with the presented network topology in Figure 3.1.

Similar to Chapter 3, the risk associated with the supply-side of blood banking networks; i.e., blood collection links, is taken into consideration. The organization attempts to minimize the total risk over all links connecting the first two tiers of the network denoted by $L_1 \subset L$. So, the risk minimization objective function for the organization is expressed as:

$$\text{Minimize} \quad \sum_{a \in L_1} \hat{r}_a(f_a), \tag{4.5}$$

where $\hat{r}_a = \hat{r}_a(f_a)$ is the total risk function on link a, and is assumed to be convex and continuously differentiable.

The supply chain network design problem for a blood banking system can be expressed as a multicriteria decision-making problem. The organization seeks to determine the optimal levels of blood processed on each supply chain network link coupled with the optimal levels of capacity escalation/reduction in its blood banking supply chain network activities subject to the minimization of the total cost (operational and discarding) as well as the minimization of the total supply risk. The weight associated with the total cost objective, (4.2), serves as the numeraire, and is set equal to 1. On

the other hand, corresponding to the total supply risk objective, (4.5), a nonnegative weight of θ is assigned by the decision-maker. Thus, the multicriteria optimization problem is:

$$\begin{aligned} \text{Minimize} \quad & \sum_{a \in L} \hat{c}_a(f_a) + \sum_{a \in L} \hat{z}_a(f_a) + \sum_{a \in L} \hat{\pi}_a(u_a) \\ & + \sum_{k=1}^{n_R} \left(\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+) \right) + \theta \sum_{a \in L_1} \hat{r}_a(f_a) \end{aligned} \tag{4.6}$$

subject to: (3.10), (3.12), (3.14), (4.3) and (4.4).

The above optimization problem is in terms of link flows. It can also be expressed in terms of path flows:

$$\begin{aligned} \text{Minimize} \quad & \sum_{p \in \mathcal{P}} \left(\hat{C}_p(x) + \hat{Z}_p(x) \right) + \sum_{a \in L} \hat{\pi}_a(u_a) \\ & + \sum_{k=1}^{n_R} \left(\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+) \right) + \theta \sum_{p \in \mathcal{P}} \hat{R}_p(x) \end{aligned} \tag{4.7}$$

subject to: (3.10), (3.12), (4.3), and (4.4).

In the above formulation, the total operational cost function, $\hat{C}_p(x)$, the total discarding cost function, $\hat{Z}_p(x)$, and the total risk function, $\hat{R}_p(x)$, corresponding to path p are as defined in (3.19a)–(3.19c). The unit cost functions on path p, i.e., $C_p(x), Z_p(x)$, and $R_p(x)$, in turn, were defined in (3.20a)–(3.20c). The preliminaries developed in (3.24) and (3.27) are also utilized to derive the first order derivatives of expected shortage and surplus values at the demand points. Furthermore, recall Lemma 3.1 that formalizes the construction of the partial derivatives of the total operational cost, the total discarding cost, and the total risk functions with respect to a path flow.

Associate the Lagrange multiplier γ_a with constraint (4.3) for link a, and denote the optimal Lagrange multiplier by $\gamma_a^*, \forall a \in L$. The Lagrange multipliers may be

interpreted as shadow prices. Group these Lagrange multipliers, respectively, into the vectors γ and γ^*.

Let K denote the feasible set such that:

$$K \equiv \{(x, u, \gamma) | x \in R_+^{n_p}, \ (4.4) \text{ holds, and } \ \gamma \in R_+^{n_L}\}. \tag{4.8}$$

I now derive the variational inequality formulation of the problem in terms of path flows and link flows.

Theorem 4.1

The optimization problem (4.7), subject to its constraints, is equivalent to the following variational inequality problem. Determine the vector of optimal path flows, the vector of optimal capacity adjustments, and the vector of optimal Lagrange multipliers $(x^*, u^*, \gamma^*) \in K$, *such that:*

$$\sum_{k=1}^{n_R} \sum_{p \in \mathcal{P}_k} \left[\frac{\partial (\sum_{q \in \mathcal{P}} \hat{C}_q(x^*))}{\partial x_p} + \frac{\partial (\sum_{q \in \mathcal{P}} \hat{Z}_q(x^*))}{\partial x_p} + \lambda_k^+ \mu_p P_k \left(\sum_{p \in \mathcal{P}_k} x_p^* \mu_p \right) \right.$$

$$\left. - \lambda_k^- \mu_p \left(1 - P_k \left(\sum_{p \in \mathcal{P}_k} x_p^* \mu_p \right) \right) + \sum_{a \in L} \gamma_a^* \delta_{ap} + \ \theta \ \frac{\partial (\sum_{q \in \mathcal{P}} \hat{R}_q(x^*))}{\partial x_p} \right] \times [x_p - x_p^*]$$

$$+ \sum_{a \in L} \left[\frac{\partial \hat{\pi}_a(u_a^*)}{\partial u_a} - \gamma_a^* \right] \times [u_a - u_a^*] + \sum_{a \in L} \left[\bar{u}_a + u_a^* - \sum_{p \in \mathcal{P}} x_p^* \alpha_{ap} \right] \times [\gamma_a - \gamma_a^*] \geq 0,$$

$$\forall (x, u, \gamma) \in K. \tag{4.9}$$

The variational inequality (4.9), in turn, can be rewritten in terms of link flows as: determine the vector of optimal link flows, the vectors of optimal projected demands

and the link capacity adjustments, and the vector of optimal Lagrange multipliers $(f^*, v^*, u^*, \gamma^*) \in K^1$, *such that:*

$$\sum_{a \in L} \left[\frac{\partial \hat{c}_a(f_a^*)}{\partial f_a} + \frac{\partial \hat{z}_a(f_a^*)}{\partial f_a} + \gamma_a^* + \theta \, \frac{\partial \hat{r}_a(f_a^*)}{\partial f_a} \right] \times [f_a - f_a^*]$$

$$+ \sum_{a \in L} \left[\frac{\partial \hat{\pi}_a(u_a^*)}{\partial u_a} - \gamma_a^* \right] \times [u_a - u_a^*] + \sum_{k=1}^{n_R} \left[\lambda_k^+ P_k(v_k^*) - \lambda_k^- (1 - P_k(v_k^*)) \right] \times [v_k - v_k^*]$$

$$+ \sum_{a \in L} [\bar{u}_a + u_a^* - f_a^*] \times [\gamma_a - \gamma_a^*] \geq 0, \qquad \forall (f, v, u, \gamma) \in K^1, \tag{4.10}$$

where K^1 *denotes the feasible set as defined below:*

$$K^1 \equiv \{(f, v, u, \gamma) | \exists x \geq 0, \ (3.12), (3.14), \text{ and } (4.4) \text{ hold, and } \gamma \geq 0\}. \tag{4.11}$$

Proof: First, I prove the result for path flows (cf. (4.9)).

The convexity of $\hat{C}_p$, $\hat{Z}_p$, and $\hat{R}_p$ for all paths p holds since $\hat{c}_a$, $\hat{z}_a$, and $\hat{r}_a$ were assumed to be convex for all links a. The convexity of $\hat{\pi}_a$ was also assumed to hold. Also, the convexity of $\lambda_k^- E(\Delta_k^-) + \lambda_k^+ E(\Delta_k^+)$ was established in Chapter 3, and the weight, θ, is nonnegative . As a consequence, the multicriteria objective function in (4.7) is also convex.

Since the objective function (4.7) is convex and the feasible set K is closed and convex, the variational inequality (4.9) follows from the standard theory of variational inequalities (see Nagurney (1999)).

As for the proof of the variational inequality (4.10), now that (4.9) is established, one can apply the equivalence between partial derivatives of total costs on paths and partial derivatives of total costs on links from Lemma 3.1. Also, from (3.12) and

(3.14), one can rewrite the formulation in terms of link flows and projected demands rather than path flows. Thus, the second part of Theorem 4.1, that is, the variational inequality in link flows (4.10), also holds. □

Similar to Chapter 3, variational inequality (4.9) can be put into standard form (cf. (2.1) and (3.43)). If the feasible set is defined as $\mathcal{K} \equiv K$, and the vector $X \equiv (x, u, \gamma)$, and $F(X) \equiv (F_1(X), F_2(X), F_3(X))$, where:

$$F_1(X) = \left[\frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x))}{\partial x_p} + \frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x))}{\partial x_p} + \lambda_k^+ \mu_p P_k \left(\sum_{p\in\mathcal{P}_k} x_p \mu_p \right) \right.$$

$$\left. -\lambda_k^- \mu_p \left(1 - P_k \left(\sum_{p\in\mathcal{P}_k} x_p \mu_p \right) \right) + \sum_{a\in L} \gamma_a \delta_{ap} + \ \theta \ \frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x))}{\partial x_p}; \right.$$

$$\left. p \in \mathcal{P}_k; \ k = 1, \ldots, n_R \right], \tag{4.12a}$$

$$F_2(X) = \left[\frac{\partial \hat{\pi}_a(u_a)}{u_a} - \gamma_a; \quad a \in L \right], \tag{4.12b}$$

and

$$F_3(X) = \left[\bar{u}_a + u_a - \sum_{p\in\mathcal{P}} x_p \alpha_{ap}; \quad a \in L \right], \tag{4.12c}$$

then variational inequality (4.9) can be re-expressed in standard form (3.43).

I utilize variational inequality (4.9) in path flows for my computations since the proposed computational procedure here will yield closed form expressions at each iteration. Once problem (4.9) is solved, by using (3.14), which relates the links flows to the path flows, one can obtain the solution f^* which, along with u^*, minimizes the total cost as well as the total supply risk (cf. (4.6)) associated with the design of the supply chain network of a blood banking system.

I now present the Euler method, adapted for the solution of the sustainable blood banking supply chain network design problem followed by several numerical examples.

4.2. The Algorithm and the Numerical Examples

In this section, similar to Chapter 3, the Euler method – presented in Chapter 2 – is utilized. Its realization for the solution of the sustainable blood bank supply chain design problem governed by variational inequality (4.9) induces subproblems that can be solved explicitly and in closed form.

Explicit Formulas for the Euler Method Applied to the Sustainable Blood Supply Chain Network Design Variational Inequality (4.9)

The procedure for the computation of solutions to the sustainable blood supply chain network design problem modeled in this chapter is now presented in the following explicit formulas. In particular, (2.47) for the blood supply chain network design problem governed by variational inequality problem (4.9) yields the following closed form expressions. At iteration $\tau + 1$, the blood product path flows, the capacity adjustments as well as the Lagrangian multipliers corresponding to various links, are respectively derived as:

$$x_p^{\tau+1} = \max\{0, x_p^\tau + a_\tau(\lambda_k^- \mu_p(1 - P_k(\sum_{p\in\mathcal{P}_k} x_p^\tau \mu_p)) - \lambda_k^+ \mu_p P_k(\sum_{p\in\mathcal{P}_k} x_p^\tau \mu_p) - \frac{\partial(\sum_{q\in\mathcal{P}} \hat{C}_q(x^\tau))}{\partial x_p} - \frac{\partial(\sum_{q\in\mathcal{P}} \hat{Z}_q(x^\tau))}{\partial x_p} - \sum_{a\in L} \gamma_a^\tau \delta_{ap} - \theta \frac{\partial(\sum_{q\in\mathcal{P}} \hat{R}_q(x^\tau))}{\partial x_p})\}, \quad \forall p \in \mathcal{P}; \quad (4.13)$$

$$u_a^{\tau+1} = \max\{-\bar{u}_a, u_a^\tau + a_\tau(\gamma_a^\tau - \frac{\partial \hat{\pi}_a(u_a^\tau)}{\partial u_a})\}, \quad \forall a \in L; \quad (4.14)$$

$$\gamma_a^{\tau+1} = \max\{0, \gamma_a^\tau + a_\tau(\sum_{p\in\mathcal{P}} x_p^\tau \alpha_{ap} - \bar{u}_a - u_a^\tau)\}, \quad \forall a \in L. \quad (4.15)$$

The initial prospective network topology used in the numerical examples of this chapter consisted of two blood collection sites, two blood centers, two component labs, two storage facilities, two distribution centers, and three demand points, as depicted in Figure 4.1. The Euler method (cf. (4.13), (4.14), and (4.15)) for the variational

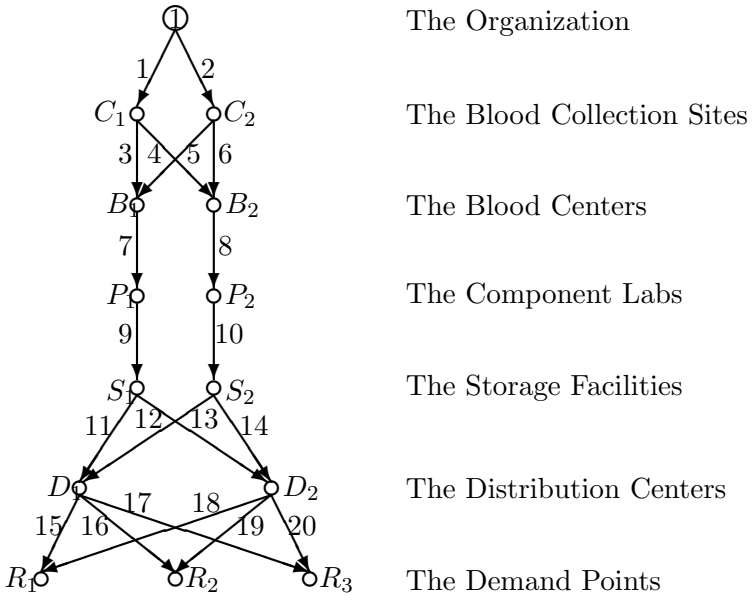

Figure 4.1. The Supply Chain Network Topology for the Numerical Examples 4.1-4.5

inequality (4.9) was implemented in Matlab to determine the solution to the numerical blood supply chain network problems in Chapter 4. A Microsoft Windows System at the University of Massachusetts Amherst was used for all the computations. I set the sequence $\{a_\tau\} = .1(1, \frac{1}{2}, \frac{1}{2}, \cdots)$, and the convergence tolerance was $\epsilon = 10^{-6}$. The algorithm was initialized by setting the projected demand at each demand point and all other variables equal to zero.

4.2.1 Example 4.1

In this example, I assumed that the existing capacities of all links in the network were zero; hence, the goal was to design a sustainable blood supply chain network from scratch.

Similar to Example 3.3, I assumed that R_1 was a small surgical center while R_2 and R_3 were large hospitals with higher demand for red blood cells. Assuming a weekly schedule for the distribution of product to these demand points, the demands

at R_1, R_2 and R_3, over the planning horizon of one week, followed a uniform probability distribution on the intervals [5,10], [40,50], and [25,40], respectively. Hence, the probability distribution functions of demand are identical to those displayed in Example 3.3.

The shortage and outdating penalties for each of the three demand points – defined by the organization, such as the American Red Cross Regional Division Management – were:

$$\lambda_1^- = 2800, \quad \lambda_1^+ = 50,$$

$$\lambda_2^- = 3000, \quad \lambda_2^+ = 60,$$

$$\lambda_3^- = 3100, \quad \lambda_3^+ = 50.$$

The total risk functions corresponding to the blood collection links were:

$$\hat{r}_1(f_1) = 2f_1^2, \quad \text{and} \quad \hat{r}_2(f_2) = 1.5f_2^2,$$

and the weight associated with the risk criterion, θ, was 0.7.

The total cost functions corresponding to the capacity adjustment are as reported in Table 4.1. In addition, the multipliers corresponding to the links, the total cost functions, and the total discarding cost functions are also reported there. Most of these numbers have been selected based on the average historical data for the American Red Cross Northeast Division Blood Services (Rios (2010)).

Table 4.1 also provides the computed optimal solutions.

As seen in Table 4.1, the optimal capacity on link 18 was zero (and, as expected, so was its flow), which means that D_1 was the only distribution center to serve the demand point R_1. The values of the total investment cost and the cost objective criterion, (4.2), were $42,375.96$ and $135,486.43$, respectively.

Table 4.1. Total Cost, Total Discarding Cost, and Total Investment Cost Functions, and Solution for Numerical Example 4.1

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	f_a^*	u_a^*	γ_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	$.8u_1^2 + u_1$	47.18	47.18	76.49
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	$.6u_2^2 + u_2$	39.78	39.78	48.73
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	$u_3^2 + 2u_3$	25.93	25.93	53.86
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	$2u_4^2 + u_4$	19.38	19.38	78.51
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	$u_5^2 + u_5$	18.25	18.25	37.50
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	$1.5u_6^2 + 3u_6$	20.74	20.74	65.22
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	$7u_7^2 + 12u_7$	43.92	43.92	626.73
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	$6u_8^2 + 20u_8$	36.73	36.73	460.69
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	$3u_9^2 + 2u_9$	38.79	38.79	234.74
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	$5.4u_{10}^2 + 2u_{10}$	34.56	34.56	375.18
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	$u_{11}^2 + u_{11}$	25.90	25.90	52.80
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	$1.5u_{12}^2 + u_{12}$	12.11	12.11	37.34
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	$1.8u_{13}^2 + 1.5u_{13}$	17.62	17.62	64.92
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	$u_{14}^2 + 2u_{14}$	16.94	16.94	35.88
15	1.00	$.4f_{15}^2 + f_{15}$	$.7f_{15}^2$	$.5u_{15}^2 + 1.1u_{15}$	5.06	5.06	6.16
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	$.7u_{16}^2 + 3u_{16}$	24.54	24.54	37.36
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	$2u_{17}^2 + u_{17}$	13.92	13.92	56.66
18	1.00	$.7f_{18}^2 + f_{18}$	$.7f_{18}^2$	$u_{18}^2 + u_{18}$	0.00	0.00	1.00
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	$u_{19}^2 + 2u_{19}$	15.93	15.93	33.86
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	$.8u_{20}^2 + u_{20}$	12.54	12.54	21.06

The computed amounts of projected demand for each of the three demand points were:

$$v_1^* = 5.06, \quad v_2^* = 40.48, \quad \text{and} \quad v_3^* = 25.93.$$

It is interesting to note that for all the demand points, the values of the projected demand were closer to the lower bounds of their uniform probability distributions due to the relatively high cost of setting up a new blood supply chain network from scratch.

Next, the effect of increasing the shortage penalties is examined – while retaining the other costs – with the purpose of reducing the risk of having shortages at the demand points.

4.2.2 Example 4.2

Example 4.2 had the exact same data as Example 4.1 with the exception of the penalties per unit shortage. The new penalties corresponding to the demand points 1,2, and 3 were as follows:

$$\lambda_1^- = 28000, \qquad \lambda_2^- = 30000, \qquad \lambda_3^- = 31000.$$

Table 4.2 shows the optimal solution for Example 4.2; that is, when the shortage penalties are ten times larger than those of Example 4.1.

Table 4.2. Total Cost, Total Discarding Cost, and Total Investment Cost Functions, and Solution for Numerical Example 4.2

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	f_a^*	u_a^*	γ_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	$.8u_1^2 + u_1$	63.53	63.53	102.65
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	$.6u_2^2 + u_2$	53.53	53.53	65.23
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	$u_3^2 + 2u_3$	34.93	34.93	71.85
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	$2u_4^2 + u_4$	26.08	26.08	105.34
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	$u_5^2 + u_5$	24.50	24.50	50.00
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	$1.5u_6^2 + 3u_6$	27.96	27.96	86.89
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	$7u_7^2 + 12u_7$	59.08	59.08	839.28
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	$6u_8^2 + 20u_8$	49.48	49.48	613.92
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	$3u_9^2 + 2u_9$	52.18	52.18	315.05
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	$5.4u_{10}^2 + 2u_{10}$	46.55	46.55	504.85
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	$u_{11}^2 + u_{11}$	35.01	35.01	71.03
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	$1.5u_{12}^2 + u_{12}$	16.12	16.12	49.36
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	$1.8u_{13}^2 + 1.5u_{13}$	23.93	23.93	87.64
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	$u_{14}^2 + 2u_{14}$	22.63	22.63	47.25
15	1.00	$.4f_{15}^2 + f_{15}$	$.7f_{15}^2$	$.5u_{15}^2 + 1.1u_{15}$	9.33	9.33	10.43
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	$.7u_{16}^2 + 3u_{16}$	29.73	29.73	44.62
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	$2u_{17}^2 + u_{17}$	19.89	19.89	80.55
18	1.00	$.7f_{18}^2 + f_{18}$	$.7f_{18}^2$	$u_{18}^2 + u_{18}$	0.00	0.00	1.00
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	$u_{19}^2 + 2u_{19}$	18.99	18.99	39.97
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	$.8u_{20}^2 + u_{20}$	18.98	18.98	31.37

A comparison of the optimal capacities in Examples 4.1 and 4.2 confirms that raising the shortage penalties, while keeping all operational and investment costs constant, increased the level of activities in all the network links, except for link 18

which stayed inactive. Due to the increased capacities, the new projected demand values were:

$$v_1^* = 9.33, \quad v_2^* = 48.71, \quad \text{and} \quad v_3^* = 38.09.$$

As seen above, unlike Example 4.1, here the projected demand values were closer to the upper bounds of their uniform probability distributions. As a result, the values of the total investment cost and the cost objective criterion, were $75,814.03$ and $177,327.31$, respectively, which were significantly higher than Example 4.1.

4.2.3 Example 4.3

In this example, I assumed positive capacities for all the activities of the supply chain network. Thus, the problem became one of redesigning an existing blood supply chain network as opposed to designing one from scratch.

The existing capacity for each link, $\bar{u}_a$, was chosen close to the corresponding optimal solution for capacity, u_a^*, in Example 4.1, as reported in Table 4.3. All other parameters were the same as in Example 4.1.

As expected, in Example 4.3, because of the positive link capacities a priori, the computed values of capacity adjustment, u_a^*, were relatively small. Therefore, the optimal Lagrangian multipliers, γ_a^*, which denote the shadow prices of constraints (4.3), $\forall a \in L$, were considerably smaller than their counterparts in Example 4.1. Furthermore, the respective values of the capacity investment cost and the cost criterion were 856.36 and $85,738.13$.

It is also important to note that, for links 14 and 20, the optimal amounts of capacity adjustment were negative, meaning that the existing capacities were slightly higher than the optimal levels given the probability distribution demands.

The Euler method in Example 4.3 computed the following projected demand values:

$$v_1^* = 6.62, \quad v_2^* = 43.50, \quad \text{and} \quad v_3^* = 30.40.$$

Table 4.3. Total Cost, Total Discarding Cost, and Total Investment Cost Functions, Initial Capacities, and Solution for Numerical Example 4.3

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	$\bar{u}_a$	f_a^*	u_a^*	γ_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	$.8u_1^2 + u_1$	48.00	54.14	6.14	10.83
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	$.6u_2^2 + u_2$	40.00	43.85	3.85	5.62
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	$u_3^2 + 2u_3$	26.00	29.64	3.64	9.29
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	$2u_4^2 + u_4$	20.00	22.35	2.35	10.39
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	$u_5^2 + u_5$	19.00	20.10	1.10	3.20
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	$1.5u_6^2 + 3u_6$	21.00	22.88	1.88	8.63
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	$7u_7^2 + 12u_7$	44.00	49.45	5.45	88.41
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	$6u_8^2 + 20u_8$	37.00	41.40	4.40	72.88
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	$3u_9^2 + 2u_9$	39.00	43.67	4.67	30.04
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	$5.4u_{10}^2 + 2u_{10}$	35.00	38.95	3.95	44.70
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	$u_{11}^2 + u_{11}$	26.00	29.23	3.23	7.45
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	$1.5u_{12}^2 + u_{12}$	13.00	13.57	0.57	2.72
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	$1.8u_{13}^2 + 1.5u_{13}$	18.00	22.05	4.05	16.07
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	$u_{14}^2 + 2u_{14}$	17.00	16.90	−0.10	1.81
15	1.00	$.4f_{15}^2 + f_{15}$	$.7f_{15}^2$	$.5u_{15}^2 + 1.1u_{15}$	6.00	6.62	0.62	1.72
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	$.7u_{16}^2 + 3u_{16}$	25.00	25.73	0.73	4.03
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	$2u_{17}^2 + u_{17}$	14.00	18.92	4.92	20.69
18	1.00	$.7f_{18}^2 + f_{18}$	$.7f_{18}^2$	$u_{18}^2 + u_{18}$	0.00	0.00	0.00	1.00
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	$u_{19}^2 + 2u_{19}$	16.00	17.77	1.77	5.53
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	$.8u_{20}^2 + u_{20}$	13.00	12.10	−0.62	0.00

4.2.4 Example 4.4

Example 4.4 was another case of redesigning the blood supply chain network, this time with increased demands. The existing capacities, the shortage penalties, and the cost functions were the same as in Example 4.3.

The new demands at the three hospitals followed a uniform probability distribution on the intervals [10,17], [50,70], and [30,60], respectively. Thus, the cumulative distribution functions corresponding to the above demands were:

$$P_1\Big(\sum_{p\in\mathcal{P}_{w_1}} \mu_p x_p\Big) = \frac{\sum_{p\in\mathcal{P}_{w_1}} \mu_p x_p - 10}{7}, \qquad P_2\Big(\sum_{p\in\mathcal{P}_{w_2}} \mu_p x_p\Big) = \frac{\sum_{p\in\mathcal{P}_{w_2}} \mu_p x_p - 50}{20},$$

$$P_3\Big(\sum_{p\in\mathcal{P}_{w_3}}\mu_p x_p\Big) = \frac{\sum_{p\in\mathcal{P}_{w_3}}\mu_p x_p - 30}{30}.$$

Table 4.4 reports the corresponding cost functions as well as the computed optimal solution for Example 4.4.

Table 4.4. Total Cost, Total Discarding Cost, and Total Investment Cost Functions, Initial Capacities, and Solution for Numerical Example 4.4

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	$\bar{u}_a$	f_a^*	u_a^*	γ_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	$.8u_1^2 + u_1$	48.00	65.45	17.45	28.92
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	$.6u_2^2 + u_2$	40.00	53.36	13.36	17.03
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	$u_3^2 + 2u_3$	26.00	35.87	9.87	21.74
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	$2u_4^2 + u_4$	20.00	26.98	6.98	28.91
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	$u_5^2 + u_5$	19.00	24.43	5.43	11.86
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	$1.5u_6^2 + 3u_6$	21.00	27.87	6.87	23.60
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	$7u_7^2 + 12u_7$	44.00	59.94	15.94	234.92
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	$6u_8^2 + 20u_8$	37.00	50.21	13.21	178.39
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	$3u_9^2 + 2u_9$	39.00	52.94	13.94	85.77
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	$5.4u_{10}^2 + 2u_{10}$	35.00	47.24	12.24	134.64
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	$u_{11}^2 + u_{11}$	26.00	35.68	9.68	20.35
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	$1.5u_{12}^2 + u_{12}$	13.00	16.20	3.20	10.61
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	$1.8u_{13}^2 + 1.5u_{13}$	18.00	26.54	8.54	32.23
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	$u_{14}^2 + 2u_{14}$	17.00	20.70	3.70	9.40
15	1.00	$.4f_{15}^2 + f_{15}$	$.7f_{15}^2$	$.5u_{15}^2 + 1.1u_{15}$	6.00	10.30	4.30	5.40
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	$.7u_{16}^2 + 3u_{16}$	25.00	30.96	5.96	11.34
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	$2u_{17}^2 + u_{17}$	14.00	20.95	6.95	28.81
18	1.00	$.7f_{18}^2 + f_{18}$	$.7f_{18}^2$	$u_{18}^2 + u_{18}$	0.00	0.35	0.35	1.69
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	$u_{19}^2 + 2u_{19}$	16.00	21.68	5.68	13.36
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	$.8u_{20}^2 + u_{20}$	13.00	14.14	1.14	2.83

As seen in Table 4.4, a 50% increase in demand resulted in significant positive capacity changes as well as positive flows on all 20 links in the network, including link 18, which was not constructed/used under the initial demand scenarios. The values of the total investment function and the cost criterion were $5,949.18$ and $166,445.73$, respectively, and the projected demand values were now:

$$v_1^* = 10.65, \quad v_2^* = 52.64, \quad \text{and} \quad v_3^* = 34.39.$$

4.2.5 Example 4.5

Example 4.5 was similar to Example 4.4, but now the demand suffered a decrease from the original demand scenario rather than the increase that was studied in Example 4.4. The new demand at demand points 1, 2, and 3 followed a uniform probability distribution on the intervals [4,7], [30, 40], and [15,30], respectively, with the following functions:

$$P_1\Big(\sum_{p\in\mathcal{P}_{w_1}}\mu_p x_p\Big)=\frac{\sum_{p\in\mathcal{P}_{w_1}}\mu_p x_p-4}{3},\qquad P_2\Big(\sum_{p\in\mathcal{P}_{w_2}}\mu_p x_p\Big)=\frac{\sum_{p\in\mathcal{P}_{w_2}}\mu_p x_p-30}{10},$$

$$P_3\Big(\sum_{p\in\mathcal{P}_{w_3}}\mu_p x_p\Big)=\frac{\sum_{p\in\mathcal{P}_{w_3}}\mu_p x_p-15}{15}.$$

Table 4.5 displays the optimal solution to this example.

As expected, most of the computed capacity changes were negative as a result of the diminished demand for blood at the demand points. Accordingly, the projected demand values were as follows:

$$v_1^*=5.52,\quad v_2^*=35.25,\quad \text{and}\quad v_3^*=23.02.$$

The value of the total cost criterion for this Example was $51,221.32$.

Table 4.5. Total Cost, Total Discarding Cost, and Total Investment Cost Functions, Initial Capacities, and Solution for Numerical Example 4.5

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	$\hat{\pi}_a(u_a)$	$\bar{u}_a$	f_a^*	u_a^*	γ_a^*
1	.97	$6f_1^2 + 15f_1$	$.8f_1^2$	$.8u_1^2 + u_1$	48.00	43.02	−0.62	0.00
2	.99	$9f_2^2 + 11f_2$	$.7f_2^2$	$.6u_2^2 + u_2$	40.00	34.54	−0.83	0.00
3	1.00	$.7f_3^2 + f_3$	$.6f_3^2$	$u_3^2 + 2u_3$	26.00	23.77	−1.00	0.00
4	.99	$1.2f_4^2 + f_4$	$.8f_4^2$	$2u_4^2 + u_4$	20.00	17.54	−0.25	0.00
5	1.00	$f_5^2 + 3f_5$	$.6f_5^2$	$u_5^2 + u_5$	19.00	15.45	−0.50	0.00
6	1.00	$.8f_6^2 + 2f_6$	$.8f_6^2$	$1.5u_6^2 + 3u_6$	21.00	18.40	−1.00	0.00
7	.92	$2.5f_7^2 + 2f_7$	$.5f_7^2$	$7u_7^2 + 12u_7$	44.00	38.99	−0.86	0.00
8	.96	$3f_8^2 + 5f_8$	$.8f_8^2$	$6u_8^2 + 20u_8$	37.00	32.91	−1.67	0.00
9	.98	$.8f_9^2 + 6f_9$	$.4f_9^2$	$3u_9^2 + 2u_9$	39.00	34.43	−0.33	0.00
10	1.00	$.5f_{10}^2 + 3f_{10}$	$.7f_{10}^2$	$5.4u_{10}^2 + 2u_{10}$	35.00	30.96	−0.19	0.00
11	1.00	$.3f_{11}^2 + f_{11}$	$.3f_{11}^2$	$u_{11}^2 + u_{11}$	26.00	23.49	−0.50	0.00
12	1.00	$.5f_{12}^2 + 2f_{12}$	$.4f_{12}^2$	$1.5u_{12}^2 + u_{12}$	13.00	10.25	−0.33	0.00
13	1.00	$.4f_{13}^2 + 2f_{13}$	$.3f_{13}^2$	$1.8u_{13}^2 + 1.5u_{13}$	18.00	18.85	0.85	4.57
14	1.00	$.6f_{14}^2 + f_{14}$	$.4f_{14}^2$	$u_{14}^2 + 2u_{14}$	17.00	12.11	−1.00	0.00
15	1.00	$.4f_{15}^2 + f_{15}$	$.7f_{15}^2$	$.5u_{15}^2 + 1.1u_{15}$	6.00	5.52	−0.48	0.63
16	1.00	$.8f_{16}^2 + 2f_{16}$	$.4f_{16}^2$	$.7u_{16}^2 + 3u_{16}$	25.00	20.68	−2.14	0.00
17	.98	$.5f_{17}^2 + 3f_{17}$	$.5f_{17}^2$	$2u_{17}^2 + u_{17}$	14.00	16.15	2.15	9.59
18	1.00	$.7f_{18}^2 + f_{18}$	$.7f_{18}^2$	$u_{18}^2 + u_{18}$	0.00	0.00	0.00	1.00
19	1.00	$.6f_{19}^2 + 4f_{19}$	$.4f_{19}^2$	$u_{19}^2 + 2u_{19}$	16.00	14.58	−1.00	0.00
20	.98	$1.1f_{20}^2 + 5f_{20}$	$.5f_{20}^2$	$.8u_{20}^2 + u_{20}$	13.00	7.34	−0.62	0.00

4.3. Summary and Conclusions

In this chapter, I developed a sustainable supply chain network design/redesign model for highly perishable human blood. The process incorporated the determination of the optimal capacities of the various activities of a blood banking system, consisting of such activities as the procurement of, the testing and processing of, and the distribution of this product. In addition to the features presented in Chapter 3, the model has some other novel properties:

It determines the optimal enhancement/reduction associated with the link capacities of existing blood banks; it allows for the determination of capacities from scratch; and it can capture the cost-related effects of shutting down specific modules of the supply chain due to an economic crisis.

The model was illustrated through several numerical examples to demonstrate the generality of this sustainable supply chain network design model for blood banking systems. A variational inequality approach was used for both model formulation and solution that establishes the foundations that enable further extensions and applications. The framework developed in this chapter – and in Chapter 3 – can be applied, with appropriate adaptation, to other perishable products, such as medicines – as demonstrated in Chapter 5 – as well as to agricultural products, including food (Yu and Nagurney (2013)).

CHAPTER 5

SUPPLY CHAIN GENERALIZED NETWORK OLIGOPOLY MODEL FOR PHARMACEUTICALS UNDER BRAND DIFFERENTIATION AND PERISHABILITY

In Chapters 3 and 4, the network operations management model and the network design model of a perishable product – that of human blood – were developed. In those chapters, a single organization – typically of non-profit type – was in charge of supplying to various demand points, and the ultimate goal was to minimize the total costs while satisfying the uncertain demand. In contrast, in this chapter, several profit-maximizing firms compete for a larger market share of a perishable product. More specifically, a generalized network oligopoly model is proposed for supply chains of pharmaceutical products. I consider the case of oligopolistic competition among the manufacturers of medication drugs where the consumers differentiate among the products of the firms, whether branded or generic. The approach quantifies several significant issues of pharmaceutical firms and includes the discarding cost associated with the wasted/perished products. The modeling and computational framework allows for the investigation of the common, yet complex, challenge faced by the pharmaceutical industry, where an expensive brand loses its dominant market share as a consequence of patent rights expiration.

This chapter is based on Masoumi, Yu, and Nagurney (2012) with additional results. The organization of this chapter is as follows. In Section 5.1, the supply chain generalized network oligopoly model with perishability and brand differentiation is developed and variational inequality formulations are derived. I discuss special

cases of the model and relate them to models that have appeared in the literature followed by the presentation of qualitative properties of the model. Then a projected dynamical system (PDS) version of the model is constructed. In Section 5.2, the Euler method (cf. Section 2.6) adapted for the pharmaceutical oligopoly problem is presented, which then is applied to several numerical cases. Section 5.3 displays a set of graphical depictions corresponding to the trajectory of solution iterates. A summary and conclusions are presented in Section 5.4.

5.1. The Supply Chain Generalized Network Oligopoly Model for Pharmaceuticals

In this model, there are I pharmaceutical firms, with a typical firm denoted by i. The firms compete noncooperatively, in an oligopolistic manner, and the consumers can differentiate among the products of the pharmaceutical firms through their individual product brands. The supply chain network activities include manufacturing, shipment, storage, and, ultimately, the distribution of the brand name drugs to the demand markets.

The proposed supply chain network model can be applied to similar cases of oligopolistic competition in which a finite number of firms provide perishable products (e.g. Yu and Nagurney (2013)). However, proper minor modifications may have to be made in order to address differences in the supply chain network topologies in related industries.

Consider the supply chain network topology presented in Figure 5.1. Each pharmaceutical firm i; $i = 1, \ldots, I$, utilizes n_M^i manufacturing plants and n_D^i distribution/storage facilities, and the goal is to serve n_R demand markets consisting of pharmacies, retail stores, hospitals, and other medical centers.

L^i denotes the set of directed links corresponding to the sequence of activities associated with firm i. Also, $G = [N, L]$ denotes the graph composed of the set of nodes N, and the set of links L, where L contains all sets of L_is: $L \equiv \cup_{i=1,\ldots,I} L^i$.

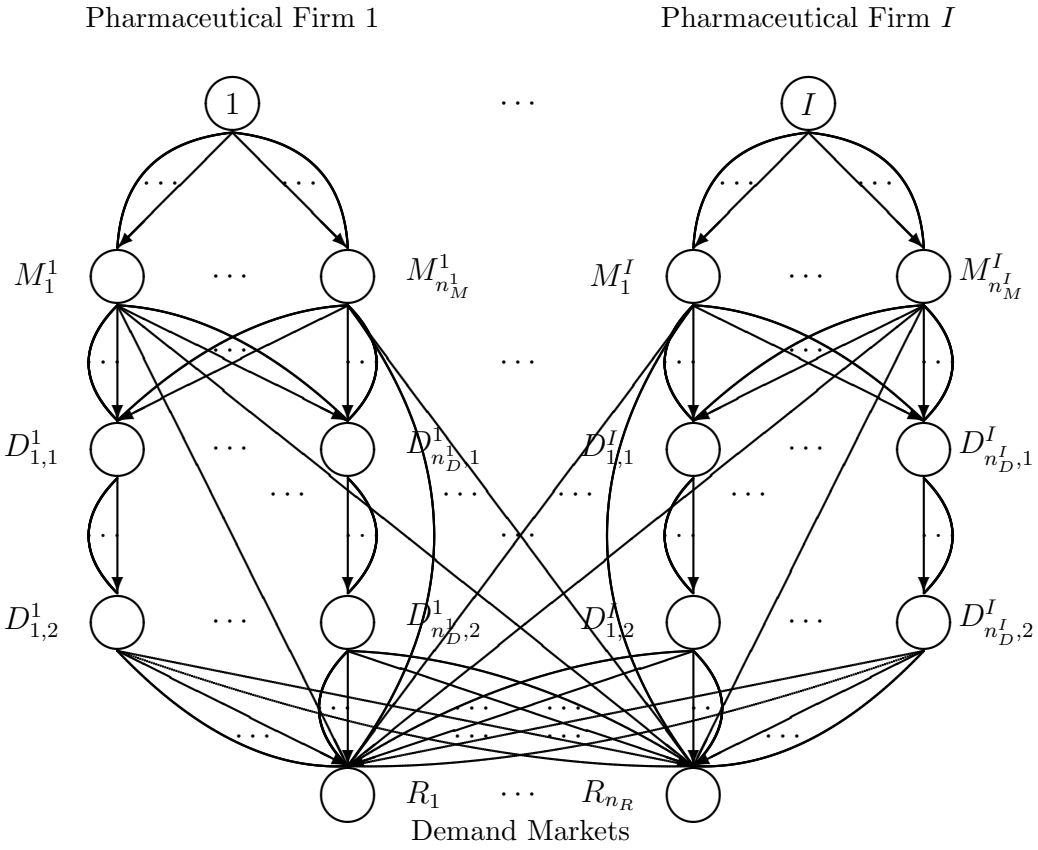

Figure 5.1. The Pharmaceutical Supply Chain Network Topology

In Figure 5.1, the first set of links connecting the top two tiers of nodes corresponds to the process of production of the drugs at each of the manufacturing units of firm i; $i = 1, \ldots, I$. Such facilities are denoted by $M_1^i, \ldots, M_{n_M^i}^i$, respectively, for firm i. Note that I allow for multiple possible links connecting each top tier node i with its manufacturing facilities, $M_1^i, \ldots, M_{n_M^i}^i$, in order to represent different possible manufacturing technologies that may be associated with a given facility. It is emphasized that the manufacturing facilities may be located not only in different regions of the same country but also in different countries.

The next set of nodes represents the distribution centers, and, thus, the links connecting the manufacturing nodes to the distribution centers are shipment-type links. Such distribution nodes associated with firm i; $i = 1, \ldots, I$ are denoted by $D^i_{1,1}, \ldots, D^i_{n^i_D,1}$ and represent the distribution centers that the produced drugs are shipped to, and stored at, before being delivered to the demand markets. There are alternative shipment links to denote different possible modes of transportation. In the shipment of pharmaceuticals that are perishable one may wish, for example, to ship by air, but at a higher cost.

The next set of links connecting nodes $D^i_{1,1}, \ldots, D^i_{n^i_D,1}$ to $D^i_{1,2}, \ldots, D^i_{n^i_D,2}; i = 1, \ldots, I$ represents the process of storage. Since drugs may require different storage conditions/technologies before being ultimately shipped to the demand markets, these alternatives are represented through multiple links at this tier.

The last set of links connecting the two bottom tiers of the supply chain network corresponds to distribution links over which the stored products are shipped from the distribution/storage facilities to the demand markets. Here I also allow for multiple modes of shipment/transportation.

In addition, in the supply chain network topology in Figure 5.1, there are direct links connecting manufacturing units with various demand markets in order to capture the possibility of direct mail shipments from manufacturers and the costs should be adjusted (see below) accordingly. While representing a small percentage of the total filled prescriptions (about 6.1 percent in 2004), mail-order pharmacy sales remained the fastest-growing sector of the US prescription drug retail market in 2004, increasing by 18 percent over the preceding year (The Health Strategies Consultancy LLC (2005)).

In this model, the perishability of the pharmaceuticals is taken into account. Although pharmaceutical products may have different life-times, similar to the models in Chapters 3 and 4, a multiplier can be assigned to each activity/link of the supply

chain to represent the fraction of the product that may perish/be wasted/be lost over the course of that activity. The fraction of lost product depends on the type of the activity since various processes of manufacturing, shipment, storage, and distribution may result in dissimilar amounts of losses. In addition, this fraction need not be the same among various links of the same tier in the supply chain network since different firms and even different units of the same firm may experience non-identical amounts of waste, depending on the brand of drug, the efficiency of the utilized technology, and the experience of the staff, etc. Also, such multipliers can capture pilferage/theft, a significant issue in drug supply chains.

The equations governing the perishability over the links are identical to those of blood supply chains – albeit with different values for arc multipliers. Please refer to equations (3.7)-(3.9) for the relationships between initial and terminal link flows, as well as the definition of total cost functions associated with the disposal of waste. Also, equations (3.11) and (3.13) define throughput factors on paths, and the arc multipliers with respect to their corresponding paths.

Let x_p represent the (initial) flow of the pharmaceutical on path p joining an origin node, i, with a destination node, R_k. The path flows must be nonnegative, that is,

$$x_p \geq 0, \qquad \forall p \in P_k^i;\ i = 1, \ldots, I; k = 1, \ldots, n_R, \tag{5.1}$$

where P_k^i is the set of all paths joining the origin node i; $i = 1, \ldots, I$ with destination node R_k.

Hence, the relationship between the link flow, f_a, and the path flows x_ps can be expressed as:

$$f_a = \sum_{i=1}^{I} \sum_{k=1}^{n_R} \sum_{p \in P_k^i} x_p\ \alpha_{ap}, \qquad \forall a \in L. \tag{5.2}$$

The arc multipliers may be obtained from historical and statistical data. They may also, in the case of certain perishable products, be related to an exponential time

decay function where the time, in my framework, is associated with each specific link activity (see, for instance, Blackburn and Scudder (2009), Bai and Kendall (2008) and Yu and Nagurney (2013)). In addition, Nagurney and Nagurney (2012) constructed explicit arc multipliers for molybdenum, which is used in nuclear medicine, which were based on the physics of time decay for this pharmaceutical product used in cancer and cardiac diagnostics, among other procedures.

Let d_{ik} denote the demand for pharmaceutical firm i's brand drug; $i = 1, \ldots, I$, at demand market R_k; $k = 1, \ldots, n_R$. The consumers differentiate the products by their brands.

The following equation reveals the relationship between the path flows and the demands in the supply chain network:

$$\sum_{p \in P_k^i} x_p \mu_p = d_{ik}, \quad i = 1, \ldots, I; k = 1, \ldots, n_R, \tag{5.3}$$

that is, the demand for a brand drug at the demand market R_k is equal to the sum of all the final flows – subject to perishability – on paths joining (i, R_k). The demands d_{ik}; $i = 1, \ldots, I; k = 1, \ldots, n_R$ are grouped into the $n_R \times I$-dimensional vector d. Note that, in this model the demands are variables. I, subsequently, show how the fixed demand case is a special case of this model.

A demand price function is associated with each firm's pharmaceutical at each demand market. Denote the demand price of firm i's product at demand market R_k by ρ_{ik} and assume that

$$\rho_{ik} = \rho_{ik}(d), \quad i = 1, \ldots, I; k = 1, \ldots, n_R. \tag{5.4}$$

Note that the price of firm i's product at a particular demand market may depend not only on the demands for its product at the other demand markets, but also on the demands for the other substitutable drugs at all the demand markets. These

demand price functions are assumed to be continuous, continuously differentiable, and monotone decreasing.

The total operational cost on link a may, in general, depend upon the product flows on all the links, that is,

$$\hat{c}_a = \hat{c}_a(f), \quad \forall a \in L, \tag{5.5}$$

where f is the vector of all the link flows. Such total cost expressions address the competition among various firms for resources used in the manufacturing, storage, and distribution of the pharmaceutical products. The total cost on each link is assumed to be convex and continuously differentiable.

X_i denotes the vector of path flows associated with firm i; $i = 1, \ldots, I$, where $X_i \equiv \{\{x_p\} | p \in P^i\} \in R_+^{n_{P^i}}$, and $P^i \equiv \cup_{k=1,\ldots,n_R} P_k^i$. In turn, n_{P^i}, denotes the number of paths from firm i to the demand markets. Thus, X is the vector of all the firms strategies, that is, $X \equiv \{\{X_i\} | i = 1, \ldots, I\}$.

The profit function of a pharmaceutical firm is defined as the difference between its revenue and it total costs, where the revenue is equal to the summation of the price times the terminal flows at each demand market. The total costs are composed of the total operational costs as well as the total discarding costs of waste over all the links in the supply chain network under control by each firm. Hence, the profit function of firm i, denoted by U_i, is expressed as:

$$U_i = \sum_{k=1}^{n_R} \rho_{ik}(d) \sum_{p \in P_k^i} \mu_p x_p - \sum_{a \in L^i} \hat{c}_a(f) - \sum_{a \in L^i} \hat{z}_a(f_a). \tag{5.6}$$

In lieu of the conservation of flow expressions (5.2) and (5.3), and the functional expressions (3.9), (5.4), and (5.5), $\hat{U}_i(X) = U_i$ can be defined for all firms i; where

$i = 1, \ldots, I$, with the I-dimensional vector $\hat{U}$ being the vector of the profits of all the firms:

$$\hat{U} = \hat{U}(X). \tag{5.7}$$

In the Cournot-Nash oligopolistic market framework, each firm selects its product path flows in a noncooperative manner, seeking to maximize its own profit, until an equilibrium is achieved, according to the definition below.

Definition 5.1: Supply Chain Generalized Network Cournot-Nash Equilibrium

Recall the definition of Nash Equilibrium in Chapter 2 (cf. Definition 8.2). A path flow pattern $X^* \in K = \prod_{i=1}^{I} K_i$ *constitutes a supply chain generalized network Cournot-Nash equilibrium if for each firm* i; $i = 1, \ldots, I$:

$$\hat{U}_i(X_i^*, \hat{X}_i^*) \geq \hat{U}_i(X_i, \hat{X}_i^*), \quad \forall X_i \in K_i, \tag{5.8}$$

where $\hat{X}_i^* \equiv (X_1^*, \ldots, X_{i-1}^*, X_{i+1}^*, \ldots, X_I^*)$ *and* $K_i \equiv \{X_i | X_i \in R_+^{n_{P^i}}\}$.

In other words, an equilibrium is established if no firm can unilaterally improve its profit by changing its production path flows, given the production path flow decisions of the other firms.

Next, the variational inequality formulations of the Cournot-Nash equilibrium are derived for the pharmaceutical supply chain network under oligopolistic competition satisfying Definition 5.1, in terms of both path flows and link flows (see Cournot (1838), Nash (1950, 1951), Gabay and Moulin (1980), and Nagurney (2006)).

Theorem 5.1

Assume that, for each pharmaceutical firm i; $i = 1, \ldots, I$, *the profit function* $\hat{U}_i(X)$ *is concave with respect to the variables in* X_i, *and is continuously differentiable. Then*

$X^* \in K$ is a supply chain generalized network Cournot-Nash equilibrium according to Definition 5.1 if and only if it satisfies the variational inequality:

$$-\sum_{i=1}^{I}\langle \nabla_{X_i}\hat{U}_i(X^*)^T, X_i - X_i^*\rangle \geq 0, \quad \forall X \in K, \tag{5.9}$$

where $\langle\cdot,\cdot\rangle$ denotes the inner product in the corresponding Euclidean space and $\nabla_{X_i}\hat{U}_i(X)$ denotes the gradient of $\hat{U}_i(X)$ with respect to X_i (also, see (2.37)) . Variational inequality (5.9), in turn, for the model, is equivalent to the variational inequality: determine $x^* \in K^1$ such that:

$$\sum_{i=1}^{I}\sum_{k=1}^{n_R}\sum_{p\in P_k^i}\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_p} + \frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_p} - \rho_{ik}(x^*)\mu_p\right.$$

$$\left. - \sum_{l=1}^{n_R}\frac{\partial\rho_{il}(x^*)}{\partial d_{ik}}\mu_p\sum_{p\in P_l^i}\mu_p x_p^*\right] \times [x_p - x_p^*] \geq 0, \quad \forall x \in K^1, \tag{5.10}$$

where $K^1 \equiv \{x | x \in R_+^{n_P}\}$, and, for notational convenience, denote:

$$\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x))}{\partial x_p} \equiv \sum_{b\in L^i}\sum_{a\in L^i}\frac{\partial\hat{c}_b(f)}{\partial f_a}\alpha_{ap} \quad \text{and} \quad \frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x))}{\partial x_p} \equiv \sum_{a\in L^i}\frac{\partial\hat{z}_a(f_a)}{\partial f_a}\alpha_{ap}. \tag{5.11}$$

Variational inequality (5.10) can also be re-expressed in terms of link flows as: determine the vector of equilibrium link flows and the vector of equilibrium demands $(f^*, d^*) \in K^2$, such that:

$$\sum_{i=1}^{I}\sum_{a\in L^i}\left[\sum_{b\in L^i}\frac{\partial\hat{c}_b(f^*)}{\partial f_a} + \frac{\partial\hat{z}_a(f_a^*)}{\partial f_a}\right] \times [f_a - f_a^*]$$

$$+\sum_{i=1}^{I}\sum_{k=1}^{n_R}\left[-\rho_{ik}(d^*) - \sum_{l=1}^{n_R}\frac{\partial\rho_{il}(d^*)}{\partial d_{ik}}d_{il}^*\right] \times [d_{ik} - d_{ik}^*] \geq 0, \quad \forall (f,d) \in K^2, \tag{5.12}$$

where $K^2 \equiv \{(f,d) | x \geq 0, and\ (5.2),\ and\ (5.3)\ hold\}$.

Proof: Variational inequality (5.9) follows directly from Gabay and Moulin (1980). See also Dafermos and Nagurney (1987). Note that

$$\nabla_{X_i}\hat{U}_i(X) = \left[\frac{\partial \hat{U}_i}{\partial x_p}; p \in P_k^i; k = 1, \ldots, n_R\right]. \tag{5.13}$$

For each path p; $p \in P_k^i$, one has:

$$\frac{\partial \hat{U}_i}{\partial x_p} = \frac{\partial \left[\sum_{l=1}^{n_R} \rho_{il}(d) \sum_{p \in P_l^i} \mu_p x_p - \sum_{b \in L^i} \hat{c}_b(f) - \sum_{b \in L^i} \hat{z}_b(f_b)\right]}{\partial x_p}$$

$$= \sum_{l=1}^{n_R} \frac{\partial \left[\rho_{il}(d) \sum_{p \in P_l^i} \mu_p x_p\right]}{\partial x_p} - \frac{\partial \left[\sum_{b \in L^i} \hat{c}_b(f)\right]}{\partial x_p} - \frac{\partial \left[\sum_{b \in L^i} \hat{z}_b(f_b)\right]}{\partial x_p}$$

$$= \rho_{ik}(d)\mu_p + \sum_{l=1}^{n_R} \frac{\partial \rho_{il}(d)}{\partial d_{ik}} \frac{\partial d_{ik}}{x_p} \sum_{p \in P_l^i} \mu_p x_p$$

$$- \sum_{a \in L^i} \frac{\partial \left[\sum_{b \in L^i} \hat{c}_b(f)\right]}{\partial f_a} \frac{\partial f_a}{\partial x_p} - \sum_{a \in L^i} \frac{\partial \left[\sum_{b \in L^i} \hat{z}_b(f_b)\right]}{\partial f_a} \frac{\partial f_a}{\partial x_p}$$

$$= \rho_{ik}(d)\mu_p + \sum_{l=1}^{n_R} \frac{\partial \rho_{il}(d)}{\partial d_{ik}} \mu_p \sum_{p \in P_l^i} \mu_p x_p - \sum_{a \in L^i} \sum_{b \in L^i} \frac{\partial \hat{c}_b(f)}{\partial f_a} \alpha_{ap} - \sum_{a \in L^i} \frac{\partial \hat{z}_a(f_a)}{\partial f_a} \alpha_{ap}. \tag{5.14}$$

Using (5.3), the demand price functions (5.4) can be re-expressed as functions of path flows. Furthermore, according to the definitions of $\frac{\partial(\sum_{q \in \mathcal{P}} \hat{C}_q(x))}{\partial x_p}$ and $\frac{\partial(\sum_{q \in \mathcal{P}} \hat{Z}_q(x))}{\partial x_p}$ in (5.11) – the equivalence of which was established in Chapter 3 – variational inequality (5.10) is established. Also, using equations (5.2) and (5.3), variational inequality (5.12) then follows from (5.10). □

Variational inequalities (5.10) and (5.12) can be put into standard form as in (2.1) and (3.43): Let: $X \equiv x$ and

$$F(X) \equiv \Big[\frac{\partial(\sum_{q \in \mathcal{P}} \hat{C}_q(x))}{\partial x_p} + \frac{\partial(\sum_{q \in \mathcal{P}} \hat{Z}_q(x))}{\partial x_p} - \rho_{ik}(x)\mu_p - \sum_{l=1}^{n_R} \frac{\partial \rho_{il}(x)}{\partial d_{ik}} \mu_p \sum_{p \in P_l^i} \mu_p x_p;$$

$$p \in P_k^i;\ i = 1, \ldots, I; k = 1, \ldots, n_R\Big], \tag{5.15}$$

and $\mathcal{K} \equiv K^1$, then (5.10) can be re-expressed as (3.43). Similarly, for the variational inequality in terms of link flows, if the following column vectors are defined: $X \equiv (f, d)$ and $F(X) \equiv (F_1(X), F_2(X))$:

$$F_1(X) = \left[\sum_{b \in L^i} \frac{\partial \hat{c}_b(f)}{\partial f_a} + \frac{\partial \hat{z}_a(f_a)}{\partial f_a};\ a \in L^i;\ i = 1, \ldots, I\right],$$

$$F_2(X) = \left[-\rho_{ik}(d) - \sum_{l=1}^{n_R} \frac{\partial \rho_{il}(d)}{\partial d_{ik}} d_{il};\ i = 1, \ldots, I; k = 1, \ldots, n_R\right], \tag{5.16}$$

and let $\mathcal{K} \equiv K^2$, then (5.12) can be re-written as (3.43).

Since the feasible set K^1 is not compact, and the same holds for K^2, one cannot obtain the existence of a solution simply based on the assumption of the continuity of F. However, considering that the demand prices should be positive, the demand d_{ik} for firm i's pharmaceutical; $i = 1, \ldots, I$ at demand market R_k; $k = 1, \ldots, n_R$, is bounded. Consequently, in light of (5.3), one has

$$\mathcal{K}_b \equiv \{x | 0 \leq x \leq b\}, \tag{5.17}$$

where $b > 0$ and $x \leq b$ means that $x_p \leq b$; $\forall p \in P_k^i$; $i = 1, \ldots, I; k = 1, \ldots, n_R$. Then $\mathcal{K}_b$ is a bounded, closed, and convex subset of $R_+^{n_p}$. Thus, the following variational inequality

$$\langle F(X^b)^T, X - X^b \rangle \geq 0, \quad \forall X \in \mathcal{K}^b, \tag{5.18}$$

admits at least one solution $X^b \in \mathcal{K}^b$, since $\mathcal{K}^b$ is compact and F is continuous. Therefore, following Kinderlehrer and Stampacchia (1980) (see also Theorem 1.5 in Nagurney (1999)), the following theorem holds:

Theorem 5.2: Existence

There exists at least one solution to variational inequality (5.10) (equivalently, to (5.12)), since there exists a $b > 0$, such that variational inequality (5.18) admits a solution in $\mathcal{K}_b$ with

$$x^b \leq b. \tag{5.19}$$

In addition, now a uniqueness result is provided.

Theorem 5.3: Uniqueness

With Theorem 5.2, variational inequality (5.18) and, hence, variational inequality (5.12) admits at least one solution. Moreover, if the function $F(X)$ of variational inequality (5.12), as defined in (5.16), is strictly monotone on $\mathcal{K} \equiv K^2$, that is,

$$\langle (F(X^1) - F(X^2))^T, X^1 - X^2 \rangle > 0, \quad \forall X^1, X^2 \in \mathcal{K}, \; X^1 \neq X^2, \tag{5.20}$$

then the solution to variational inequality (5.12) is unique, that is, the equilibrium link flow pattern and the equilibrium demand pattern are unique.

For additional details on conditions for existence and uniqueness of a Nash equilibrium, please refer to Theorems 2.7–2.11.

The above model is now related to several models in the literature. First, note that, if the arc multipliers are all equal to 1, in which case the product is not perishable, then the model is related to the sustainable fashion supply chain network model of Nagurney and Yu (2012). In that model, however, the other criterion, in addition to the profit maximization one, was emission minimization, rather than waste cost minimization, as in the model in this chapter.

If the product is homogeneous, and all the arc multipliers are, again, assumed to be equal to 1, and the total costs are assumed to be separable, then the above model

collapses to the supply chain network oligopoly model of Nagurney (2010c) in which synergies associated with mergers and acquisitions were assessed.

In addition, if there is only a single organization/firm, in which case there is no product differentiation, and the demands are subject to uncertainty, with the inclusion of expected costs due to shortages or excess supplies, the total operational cost functions are separable, and a criterion of risk is added, then the model above is related to the blood supply chain network operations management model in Chapter 3.

A simple numerical example is now presented in order to illustrate the model.

5.1.1 Example 5.1

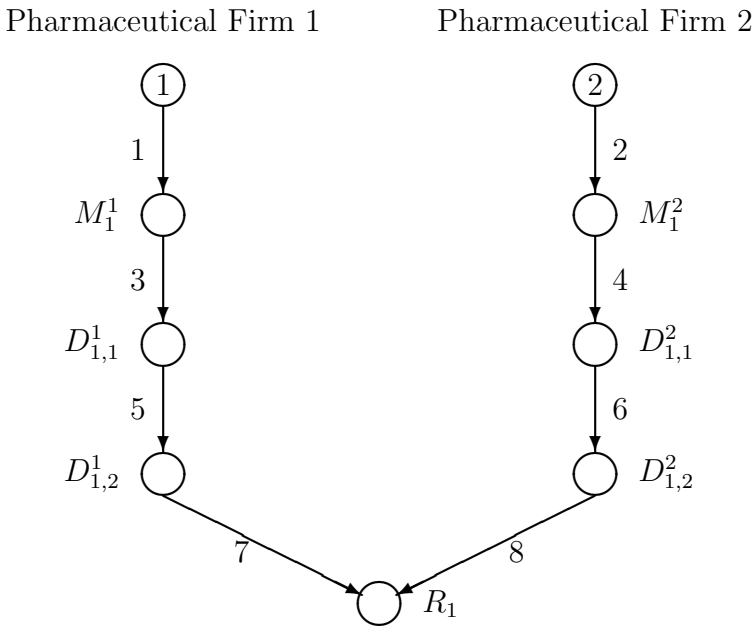

Figure 5.2. Supply Chain Network Topology for the Pharmaceutical Duopoly in Example 5.1

In this example, two pharmaceutical firms compete in a duopoly with a single demand market (See Figure 5.2). The two firms produce differentiated, but substitutable, brand drugs 1 and 2, corresponding to Firm 1 and Firm 2, respectively.

The total cost functions on the various links of manufacturing, shipment, storage, and distribution are:

$$\hat{c}_1(f_1) = 5f_1^2 + 8f_1, \quad \hat{c}_2(f_2) = 7f_2^2 + 3f_2, \quad \hat{c}_3(f_3) = 2f_3^2 + f_3, \quad \hat{c}_4(f_4) = 2f_4^2 + 2f_4,$$
$$\hat{c}_5(f_5) = 3f_5^2 + 4f_5, \quad \hat{c}_6(f_6) = 3.5f_6^2 + f_6, \quad \hat{c}_7(f_7) = 2f_7^2 + 5f_7, \quad \hat{c}_8(f_8) = 1.5f_8^2 + 4f_8.$$

The arc multipliers are given by:

$$\alpha_1 = .95, \quad \alpha_2 = .98, \quad \alpha_3 = .99, \quad \alpha_4 = 1.00,$$
$$\alpha_5 = .99, \quad \alpha_6 = .97, \quad \alpha_7 = 1.00, \quad \alpha_8 = 1.00.$$

The total discarding cost functions on the links are assumed identical, that is,

$$\hat{z}_a(f_a) = .5f_a^2, \quad \forall a.$$

The firms compete in the demand market R_1, and the consumers reveal their preferences for the two products through the following nonseparable demand price functions:

$$\rho_{11}(d) = -3d_{11} - d_{21} + 200, \quad \rho_{21}(d) = -4d_{21} - 1.5d_{11} + 300.$$

In this supply chain network, there exists one path corresponding to each firm, denoted by p_1 and p_2. Thus, variational inequality (5.10), in the case of this example, can be re-expressed as:

$$\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_1}} + \frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_{p_1}} - \rho_{11}(x^*)\mu_{p_1} - \frac{\partial\rho_{11}(x^*)}{\partial d_{11}}\mu_{p_1}\times\mu_{p_1}x^*_{p_1}\right]\times[x_{p_1} - x^*_{p_1}]$$
$$+\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_2}} + \frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_{p_2}} - \rho_{21}(x^*)\mu_{p_2} - \frac{\partial\rho_{21}(x^*)}{\partial d_{21}}\mu_{p_2}\times\mu_{p_2}x^*_{p_2}\right]$$
$$\times[x_{p_2} - x^*_{p_2}] \geq 0, \quad \forall x \in K^1. \tag{5.21}$$

Under the assumption that $x^*_{p_1} > 0$ and $x^*_{p_2} > 0$, the two expressions on the left-hand side of inequality (5.21) must be equal to zero, that is:

$$\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_1}}+\frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_{p_1}}-\rho_{11}(x^*)\mu_{p_1}-\frac{\partial\rho_{11}(x^*)}{\partial d_{11}}\mu_{p_1}\times\mu_{p_1}x^*_{p_1}\right]$$

$$\times[x_{p_1}-x^*_{p_1}]=0, \tag{5.22a}$$

and

$$\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_{p_2}}+\frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_{p_2}}-\rho_{21}(x^*)\mu_{p_2}-\frac{\partial\rho_{21}(x^*)}{\partial d_{21}}\mu_{p_2}\times\mu_{p_2}x^*_{p_2}\right]$$

$$\times[x_{p_2}-x^*_{p_2}]=0. \tag{5.22b}$$

Since each of the paths flows must be nonnegative, the term preceding the multiplication sign in both (5.22a) and (5.22b) must be equal to zero.

Calculating the values of the multipliers from (3.13), and then, substituting those values, as well as, the given functions into (5.11), one can determine the partial derivatives of the total operational cost and the total discarding cost functions in (5.22a) and (5.22b). Furthermore, the partial derivatives of the given demand price functions can be calculated and substituted into the above. Applying (3.11), the path multipliers are equal to:

$$\mu_{p_1}=\alpha_1\times\alpha_3\times\alpha_5\times\alpha_7=.95\times.99\times.99\times1=.93,$$
$$\mu_{p_2}=\alpha_2\times\alpha_4\times\alpha_6\times\alpha_8=.98\times1\times.97\times1=.95.$$

Simple arithmetic calculations, with the above substitutions, yield the below system of equations:

$$\begin{cases}31.24x^*_{p_1}+0.89x^*_{p_2}=168.85,\\ 1.33x^*_{p_1}+38.33x^*_{p_2}=274.46.\end{cases} \tag{5.23}$$

Thus, the equilibrium solution corresponding to the path flow of brand drugs produced by firms 1 and 2 is:

$$x^*_{p_1} = 5.21, \quad x^*_{p_2} = 6.98.$$

Using (5.2), the equilibrium link flows can be calculated as:

$$f^*_1 = 5.21, \quad f^*_3 = 4.95, \quad f^*_5 = 4.90, \quad f^*_7 = 4.85,$$
$$f^*_2 = 6.98, \quad f^*_4 = 6.84, \quad f^*_6 = 6.84, \quad f^*_8 = 6.64.$$

From (5.3), the equilibrium values of demand for products of the two pharmaceutical firms are equal to:

$$d^*_{11} = 4.85, \quad d^*_{21} = 6.64.$$

Finally, the equilibrium prices of the two branded drugs are:

$$\rho_{11} = 178.82, \quad \rho_{21} = 266.19.$$

Note that, even though the price of Firm 2's product is observed to be higher, the market has a slightly stronger tendency toward this product as opposed to the product of Firm 1. This is due to the willingness of the consumers to spend more on one product which can be a consequence of the reputation, or the perceived quality, of Firm 2's brand drug.

Next, 3 special cases of the model presented in this chapter are discussed.

5.1.2 Corollaries: Special Cases of the Model

Corollary 5.1

Assume that the pharmaceutical firms produce a homogeneous drug. Denote the demand for the homogeneous drug and its demand price at demand market R_k, respectively, by d_k and ρ_k, instead of by d_{ik} and ρ_{ik}. Consequently, the following equation, which replaces (5.3), must then hold:

$$\sum_{i=1}^{I} \sum_{p \in P^i_k} x_p \mu_p = d_k, \quad k = 1, \ldots, n_R. \tag{5.24}$$

Then, the profit function (5.6) can be rewritten as:

$$U_i = \sum_{k=1}^{n_R} \rho_k(d) \sum_{p \in P_k^i} \mu_p x_p - \sum_{a \in L^i} \hat{c}_a(f) - \sum_{a \in L^i} \hat{z}_a(f_a). \tag{5.25}$$

The corresponding variational inequality (5.10) in terms of path flows can be rewritten as: determine $x^* \in K^1$ such that:

$$\sum_{i=1}^{I} \sum_{k=1}^{n_R} \sum_{p \in P_k^i} \left[\frac{\partial(\sum_{q \in \mathcal{P}} \hat{C}_q(x^*))}{\partial x_p} + \frac{\partial(\sum_{q \in \mathcal{P}} \hat{Z}_q(x^*))}{\partial x_p} - \rho_k(x^*)\mu_p - \sum_{l=1}^{n_R} \frac{\partial \rho_l(x^*)}{\partial d_k} \mu_p \sum_{p \in P_l^i} \mu_p x_p^* \right]$$

$$\times [x_p - x_p^*] \geq 0, \qquad \forall x \in K^1. \tag{5.26}$$

Proof: According to the proof of Theorem 5.1, variational inequality (5.26) can be proved by replacing d_{ik} and ρ_{ik} in (5.14), respectively, by d_k and ρ_k.□

It is interesting to note that the supply chain generalized network oligopoly model presented here can also capture the competition in the pharmaceutical industry even when the demands d_{ik} are fixed, for all brands i; $i = 1, \ldots, I$, and all demand markets R_k; $k = 1, \ldots, n_R$, since total cost functions of the form in (5.5) are considered. Fixed demands for pharmaceutical products arise, for example, in the case of certain hospital and medical procedures, which need to be scheduled in advance. For example, the supply chain for medical nuclear products, as discussed in Nagurney and Nagurney (2012), is characterized by fixed demands since medical procedures that use such radioisotopes, such as, for example, molybdenum, need to be scheduled a priori; moreover, radioisotopes, since they are subject to radioactive decay are not only perishable but also time-sensitive.

Corollary 5.2

Assume that the demand d_{ik} for firm i's pharmaceutical; $i = 1, \ldots, I$, at demand market R_k; $k = 1, \ldots, n_R$, is fixed. According to the demand price function (5.4), the

demand price of firm i's product at demand market R_k will then also be fixed; denote this price by $\bar{\rho}_{ik}$. The profit function (5.6) can then be rewritten as:

$$U_i = \sum_{k=1}^{n_R} \bar{\rho}_{ik} d_{ik} - \sum_{a \in L^i} \hat{c}_a(f) - \sum_{a \in L^i} \hat{z}_a(f_a), \tag{5.27}$$

where the revenue of firm i, $\sum_{k=1}^{n_R} \bar{\rho}_{ik} d_{ik}$, is fixed. Therefore, the corresponding variational inequality (5.10) in terms of path flows simplifies, in this case, to: determine $x^* \in K^3$ such that:

$$\sum_{i=1}^{I} \sum_{k=1}^{n_R} \sum_{p \in P_k^i} \left[\frac{\partial (\sum_{q \in \mathcal{P}} \hat{C}_q(x^*))}{\partial x_p} + \frac{\partial (\sum_{q \in \mathcal{P}} \hat{Z}_q(x^*))}{\partial x_p} \right] \times [x_p - x_p^*] \geq 0, \; \forall x \in K^3, \tag{5.28}$$

where $K^3 \equiv \{x | x \geq 0,$ and (5.3) is satisfied with the d_{ik}s known and fixed, $\forall i, k.\}$. Similarly, variational inequality (5.28) can be re-expressed in terms of link flows as: determine $f^* \in K^4$, such that:

$$\sum_{i=1}^{I} \sum_{a \in L^i} \left[\sum_{b \in L^i} \frac{\partial \hat{c}_b(f^*)}{\partial f_a} + \frac{\partial \hat{z}_a(f_a^*)}{\partial f_a} \right] \times [f_a - f_a^*] \geq 0, \quad \forall f \in K^4, \tag{5.29}$$

where $K^4 \equiv \{f | \exists x \geq 0,$ and (5.2) and (5.3) are satisfied with the d_{ik}s known and fixed, $\forall i, k.\}$.

Proof: Based on the proof of Theorem 5.1, variational inequality (5.28) can be established by eliminating the corresponding term of firm i's revenue in (5.14), since the revenue of firm i, $\sum_{k=1}^{n_R} \bar{\rho}_{ik} d_{ik}$, is fixed. Also, using equation (5.2), variational inequality (5.29) follows from (5.28).□

Below, a specific case is discussed in which the pharmaceutical companies produce a homogeneous drug and the demand at each demand market is fixed.

Corollary 5.3

Assume that the pharmaceutical firms produce a homogeneous drug. Denote the demand for the homogeneous drug and its demand price at demand market R_k, respectively, by d_k and $\bar{\rho}_k$, instead of by d_{ik} and ρ_{ik}. Consequently, the following equation, which replaces (5.3), must then hold:

$$\sum_{i=1}^{I} \sum_{p \in P_k^i} x_p \mu_p = d_k, \quad k = 1, \ldots, n_R. \tag{5.30}$$

Assume also that the demand d_k at demand market R_k; $k = 1, \ldots, n_R$ is fixed, as well as the demand price $\bar{\rho}_k$. Then, the profit function (5.6) can be rewritten as:

$$U_i = \sum_{k=1}^{n_R} \bar{\rho}_k \sum_{p \in P_k^i} \mu_p x_p - \sum_{a \in L^i} \hat{c}_a(f) - \sum_{a \in L^i} \hat{z}_a(f_a). \tag{5.31}$$

The corresponding variational inequality in terms of path flows, akin to (5.28), is: determine $x^* \in K^5$ such that:

$$\sum_{i=1}^{I} \sum_{k=1}^{n_R} \sum_{p \in P_k^i} \left[\frac{\partial (\sum_{q \in \mathcal{P}} \hat{C}_q(x^*))}{\partial x_p} + \frac{\partial (\sum_{q \in \mathcal{P}} \hat{Z}_q(x^*))}{\partial x_p} \right] \times [x_p - x_p^*] \geq 0, \; \forall x \in K^5, \tag{5.32}$$

where $K^5 \equiv \{x | x \geq 0,$ and (5.30) is satisfied with the d_ks known and fixed, $\forall k.\}$.

Similarly, the corresponding variational inequality in terms of link flows, akin to (5.29), is: determine $f^* \in K^6$, such that:

$$\sum_{i=1}^{I} \sum_{a \in L^i} \left[\sum_{b \in L^i} \frac{\partial \hat{c}_b(f^*)}{\partial f_a} + \frac{\partial \hat{z}_a(f_a^*)}{\partial f_a} \right] \times [f_a - f_a^*] \geq 0, \quad \forall f \in K^6, \tag{5.33}$$

where $K^6 \equiv \{f | \exists x \geq 0,$ and (5.2) and (5.30) are satisfied with the d_ks known and fixed, $\forall k.\}$.

Proof: Following the proof of Theorem 5.1, one has:

$$\sum_{i=1}^{I}\sum_{k=1}^{n_R}\sum_{p\in P_k^i}\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_p}+\frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_p}-\bar{\rho}_k\mu_p\right]\times[x_p-x_p^*]\geq 0,\ \forall x\in K^5, \tag{5.34}$$

which is equivalent to:

$$\sum_{i=1}^{I}\sum_{k=1}^{n_R}\sum_{p\in P_k^i}\left[\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^*))}{\partial x_p}+\frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^*))}{\partial x_p}\right]\times[x_p-x_p^*]$$

$$-\sum_{k=1}^{n_R}\bar{\rho}_k\left[\sum_{i=1}^{I}\sum_{p\in P_k^i}\mu_p x_p-\sum_{i=1}^{I}\sum_{p\in P_k^i}\mu_p x_p^*\right]\geq 0,\qquad \forall x\in K^5. \tag{5.35}$$

Applying now equation (5.30) to (5.35), yields variational inequality (5.32). Also, using equation (5.2), variational inequality (5.33) then follows from (5.32). □

5.1.3 The Projected Dynamical System Model

Recall the finite-dimensional projected dynamical systems (PDS) (Definition 2.10). In this section, a dynamic adjustment process for the evolution of the pharmaceutical firms' product flows is proposed.

First, from (5.7), recall $\hat{U}=\hat{U}(X)$, i.e., the vector of firms' profits where X denotes the vector of firms' strategy variables. X, in turn, is composed of X_i's where X_i is the vector of path flows associated with firm $i; i=1,\ldots,I$.

The PDS model for the pharmaceutical supply chain oligopoly problem can be written in terms of path flows (cf. Nagurney, Dupuis, and Zhang (1994)). For each path $p\in P_k^i; i=1,\ldots,I; k=1,\ldots,n_R$, the following adjustment process is proposed for the product flow on a path:

$$\dot{x}_p=\begin{cases}\frac{\partial\hat{U}_i}{\partial x_p}, & \text{if}\quad x_p>0,\\ \max\{0,\frac{\partial\hat{U}_i}{\partial x_p}\}, & \text{if}\quad x_p=0,\end{cases} \tag{5.36}$$

where $\hat{U}_i$ denotes the profit function of firm i. Note that the partial derivative $\frac{\partial \hat{U}_i}{\partial x_p}$ was explicitly calculated in (5.14). The adjustment process in (5.36) can be interpreted as follows. Each pharmaceutical firm i updates its strategic decision variables – the flow of its product on the paths associated with that firm – unilaterally and individually with respect to the marginal profit of the firm continuously as long as the product flows on those paths are positive. If the flow on a path becomes zero, the adjustment process will be equal to the greater of zero and its marginal profit. At the equilibrium (stationary) point, there will be no change in path flows. According to Theorem 2.12, such equilibrium point of the PDS model, X^*, coincides with the solution to the variational inequality (5.10).

5.2. The Algorithm and the Case Study

The Euler method (cf. Section 2.6) is also applicable to the solution of the supply chain generalized network oligopoly model with brand differentiation governed by variational inequality (5.10). It induces subproblems that can be solved explicitly and in closed form. The Euler method can also be utilized to solve the supply chain generalized network models as in Corollaries 5.1, 5.2, and 5.3.

Explicit Formulae for the Euler Method Applied to the Supply Chain Generalized Network Oligopoly Variational Inequality (5.10)

The elegance of this procedure for the computation of solutions to the supply chain generalized network oligopoly model with product differentiation can be seen in the following explicit formulae. In particular, (2.47) in the case of variational inequality problem (5.10) yields the following closed form expressions for all the path flows $p \in P_k^i, \forall i, k$:

$$x_p^{\tau+1} = \max\Big\{0, x_p^\tau + a_\tau\Big(\rho_{ik}(x^\tau)\mu_p + \sum_{l=1}^{n_R}\frac{\partial\rho_{il}(x^\tau)}{\partial d_{ik}}\mu_p\sum_{p\in P_l^i}\mu_p x_p^\tau$$

$$-\frac{\partial(\sum_{q\in\mathcal{P}}\hat{C}_q(x^\tau))}{\partial x_p} - \frac{\partial(\sum_{q\in\mathcal{P}}\hat{Z}_q(x^\tau))}{\partial x_p}\Big)\Big\}. \tag{5.37}$$

It is emphasized that the Euler method can also be interpreted as a discrete-time adjustment process. The Euler method not only computes the stationary points of projected dynamical system but also provides a means of tracking the associated trajectories over time. This shall be seen in the case study presented in the next section.

Next, the above algorithmic scheme is applied to compute solutions to several cases of pharmaceutical supply chain network problems which are based on real world scenarios. The examples focus on cholesterol regulating drug competition in the US under various situations, including the expiration of the patent rights to a popular brand and the emergence of its generic substitute. Although the examples are stylized, they illustrate the modeling and algorithmic framework presented in this chapter. For purposes of transparency and reproducibility, both the input and the output data are provided.

5.2.1 Case I

This case is assumed occur in the third quarter of 2011 prior to the expiration of the patent for Lipitor. It was once the top-selling pharmaceutical brand worldwide with more than $5 billion of sales in the US alone in 2011 (Rossi (2011)). Firm 1 represents a multinational pharmaceutical giant, hypothetically, Pfizer, Inc., which currently possesses the patent for Lipitor.

Firm 2, on the other hand, which might represent, for example, Merck & Co., Inc., also is one of the largest global pharmaceutical companies, and has been producing Zocor, another cholesterol regulating brand, whose patent expired in 2006.

In this numerical example, the case of these two competing brands in three demand markets located across the US is considered. Each of these two firms is assumed to have two manufacturing units and three storage/distribution centers, as illustrated in Figure 5.3.

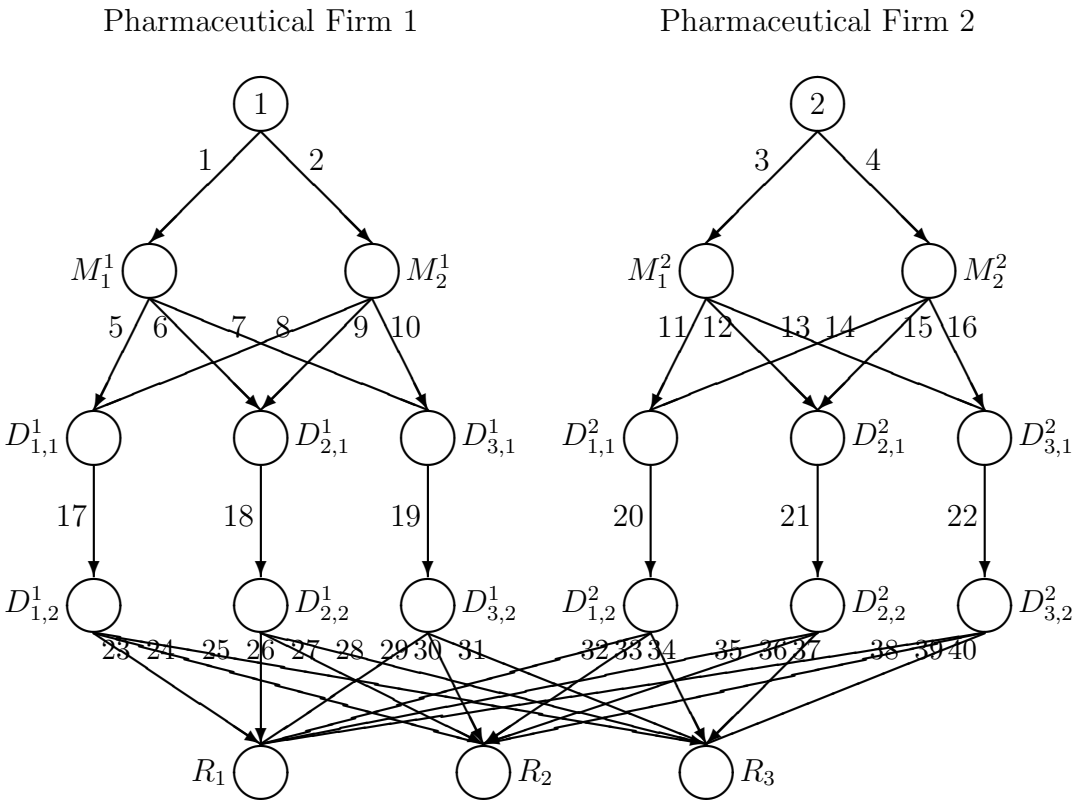

Figure 5.3. The Pharmaceutical Supply Chain Network Topology for Case I

The demand price functions corresponding to the three demand markets for each of the two brands 1 and 2 were as follows:

$$\rho_{11}(d) = -1.1d_{11} - 0.9d_{21} + 275; \qquad \rho_{21}(d) = -1.2d_{21} - 0.7d_{11} + 210;$$
$$\rho_{12}(d) = -0.9d_{12} - 0.8d_{22} + 255; \qquad \rho_{22}(d) = -1.0d_{22} - 0.5d_{12} + 200;$$
$$\rho_{13}(d) = -1.4d_{13} - 1.0d_{23} + 265; \qquad \rho_{23}(d) = -1.5d_{23} - 0.4d_{13} + 186.$$

The demand for each firm represents the number of packages of an equivalent dosage for each brand over a time period of one week.

The arc multipliers, the total operational cost functions, and the total discarding cost functions were as reported in Table 5.1. These cost functions have been selected based on the average values of the data corresponding to the prices, the shipping costs, etc., available on the web. The values of arc multipliers, in turn, although hypothetical, are constructed in order to reflect the percentage of perishability/waste/loss associated with the various supply chain network activities in medical drug supply chains.

The Euler method (cf. (5.37)) for the solution of variational inequality (5.10) was implemented in Matlab on a Microsoft Windows 7 System with a Dell PC at the University of Massachusetts Amherst. The sequence was set as $a_\tau = .1(1, \frac{1}{2}, \frac{1}{2}, \cdots)$, and the convergence tolerance was 10^{-6}. In other words, the absolute value of the difference between each path flow in two consecutive iterations was less than or equal to this tolerance. The algorithm was initialized by setting the path flows equal to 10. Table 5.1 provides the computed equilibrium link product flows of each of the two competing branded drugs on every single link in the supply chain oligopoly network. For Cases I and II, the equilibrium link flows are reported, rather than the path flows, due to space limitation.

The values of the equilibrium link flows in Table 5.1 demonstrate the impact of perishability of the product throughout the supply chain network links of each pharmaceutical firm. Under the above demand price functions, the computed equilibrium demands for each of the two brands were:

$$d_{11}^* = 10.32, \qquad d_{21}^* = 7.66,$$
$$d_{12}^* = 4.17, \qquad d_{22}^* = 8.46,$$
$$d_{13}^* = 8.41, \qquad d_{23}^* = 1.69.$$

Table 5.1. Link Multipliers, Total Operational Cost, and Total Discarding Cost Functions and Equilibrium Link Flow Solution for Case I

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	f_a^*
1	.95	$5f_1^2 + 8f_1$	$.5f_1^2$	13.73
2	.97	$7f_2^2 + 3f_2$	$.4f_2^2$	10.77
3	.96	$6.5f_3^2 + 4f_3$	$.3f_3^2$	8.42
4	.98	$5f_4^2 + 7f_4$	$.35f_4^2$	10.55
5	1.00	$.7f_5^2 + f_5$	$.5f_5^2$	5.21
6	.99	$.9f_6^2 + 2f_6$	$.5f_6^2$	3.36
7	1.00	$.5f_7^2 + f_7$	$.5f_7^2$	4.47
8	.99	$f_8^2 + 2f_8$	$.6f_8^2$	3.02
9	1.00	$.7f_9^2 + 3f_9$	$.6f_9^2$	3.92
10	1.00	$.6f_{10}^2 + 1.5f_{10}$	$.6f_{10}^2$	3.50
11	.99	$.8f_{11}^2 + 2f_{11}$	$.4f_{11}^2$	3.10
12	.99	$.8f_{12}^2 + 5f_{12}$	$.4f_{12}^2$	2.36
13	.98	$.9f_{13}^2 + 4f_{13}$	$.4f_{13}^2$	2.63
14	1.00	$.8f_{14}^2 + 2f_{14}$	$.5f_{14}^2$	3.79
15	.99	$.9f_{15}^2 + 3f_{15}$	$.5f_{15}^2$	3.12
16	1.00	$1.1f_{16}^2 + 3f_{16}$	$.6f_{16}^2$	3.43
17	.98	$2f_{17}^2 + 3f_{17}$	$.45f_{17}^2$	8.20
18	.99	$2.5f_{18}^2 + f_{18}$	$.55f_{18}^2$	7.25
19	.98	$2.4f_{19}^2 + 1.5f_{19}$	$.5f_{19}^2$	7.97
20	.98	$1.8f_{20}^2 + 3f_{20}$	$.3f_{20}^2$	6.85
21	.98	$2.1f_{21}^2 + 3f_{21}$	$.35f_{21}^2$	5.42
22	.99	$1.9f_{22}^2 + 2.5f_{22}$	$.5f_{22}^2$	6.00
23	1.00	$.5f_{23}^2 + 2f_{23}$	$.6f_{23}^2$	3.56
24	1.00	$.7f_{24}^2 + f_{24}$	$.6f_{24}^2$	1.66
25	.99	$.5f_{25}^2 + .8f_{25}$	$.6f_{25}^2$	2.82
26	.99	$.6f_{26}^2 + f_{26}$	$.45f_{26}^2$	3.34
27	.99	$.7f_{27}^2 + .8f_{27}$	$.4f_{27}^2$	1.24
28	.98	$.4f_{28}^2 + .8f_{28}$	$.45f_{28}^2$	2.59
29	1.00	$.3f_{29}^2 + 3f_{29}$	$.55f_{29}^2$	3.45
30	1.00	$.75f_{30}^2 + f_{30}$	$.55f_{30}^2$	1.28
31	1.00	$.65f_{31}^2 + f_{31}$	$.55f_{31}^2$	3.09
32	.99	$.5f_{32}^2 + 2f_{32}$	$.3f_{32}^2$	2.54
33	.99	$.4f_{33}^2 + 3f_{33}$	$.3f_{33}^2$	3.43
34	1.00	$.5f_{34}^2 + 3.5f_{34}$	$.4f_{34}^2$	0.75
35	.98	$.4f_{35}^2 + 2f_{35}$	$.55f_{35}^2$	1.72
36	.98	$.3f_{36}^2 + 2.5f_{36}$	$.55f_{36}^2$	2.64
37	.99	$.55f_{37}^2 + 2f_{37}$	$.55f_{37}^2$	0.95
38	1.00	$.35f_{38}^2 + 2f_{38}$	$.4f_{38}^2$	3.47
39	1.00	$.4f_{39}^2 + 5f_{39}$	$.4f_{39}^2$	2.47
40	.98	$.55f_{40}^2 + 2f_{40}$	$.6f_{40}^2$	0.00

Furthermore, the incurred equilibrium prices associated with the branded drugs at each demand market were as follows:

$$\rho_{11}(d^*) = 256.75, \qquad \rho_{21}(d^*) = 193.58,$$
$$\rho_{12}(d^*) = 244.48, \qquad \rho_{22}(d^*) = 189.46,$$
$$\rho_{13}(d^*) = 251.52, \qquad \rho_{23}(d^*) = 180.09.$$

Note that Firm 1, which produces the top-selling product, captures the majority of the market share at demand markets 1 and 3, despite the higher price. While this firm has a slight advantage over its competitor in demand market 1, it has almost entirely seized demand market 3. Consequently, several links connecting Firm 2 to demand market 3 have insignificant flows including link 40 with a flow equal to zero. In contrast, Firm 2 dominates demand market 2, due to the consumers' willingness to lean towards this product there, perhaps as a consequence of the lower price, or the perception of quality, etc., as compared to the product of Firm 1.

The profits of the two firms are:

$$U_1(X^*) = 2,936.52, \quad \text{and} \quad U_2(X^*) = 1,675.89.$$

Recall that Firm 1 still holds the patent rights of its branded drug, and, thus, makes a higher profit from selling cholesterol regulators. In contrast, Firm 2 has completed the competition-free timespan for its brand of cholesterol medicine a few years ago as a consequence of losing the patent rights to the manufacturers of generic drugs. Hence, fewer numbers of consumers choose this product as compared to the product of Firm 1 leading to a higher profit for the producer of the newer brand.

The next case explores the situation of the cholesterol-lowering drug market in the first quarter of 2012, when the patent right of Firm 1's product has just expired as well, and a third firm steps up to produce a generic substitute of this product.

5.2.2 Case II

In this case, I consider the scenario in which Firm 1 has just lost the exclusive patent right of its highly popular cholesterol regulator despite all the legal and political efforts to extend the patent. A manufacturer of generic drugs, say, Ranbaxy Laboratories, here denoted by Firm 3, has recently introduced a generic substitute for Lipitor by reproducing its active ingredients. Firm 3 is assumed to have two manufacturing plants, two distribution centers as well as two storage facilities in order to supply the same three demand markets as in Case I (See Figure 5.4).

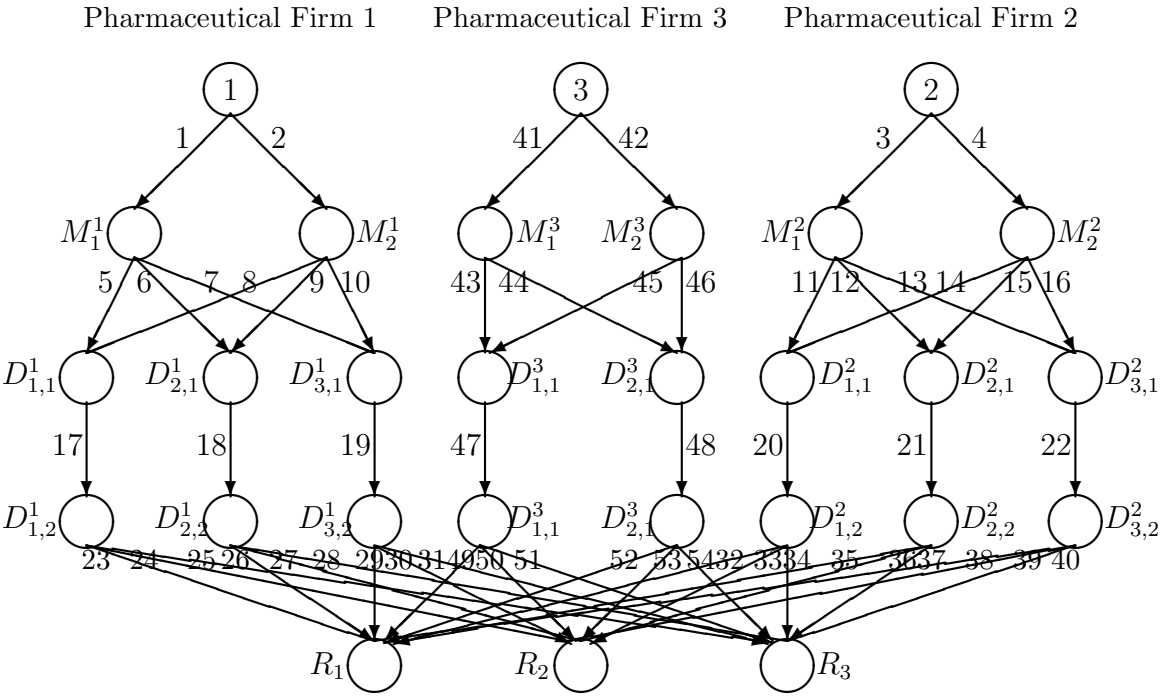

Figure 5.4. The Pharmaceutical Supply Chain Network Topology for Cases II and III

Since, in Case II, the new generic drug has just been released, it is assumed that the demand price functions for the products of Firm 1 and 2 will stay the same as in Case I. The demand price functions corresponding to the product of Firm 3 for demand markets 1, 2, and 3 are as follows:

$$\rho_{31}(d) = -0.9d_{31} - 0.6d_{11} - 0.8d_{21} + 150;$$
$$\rho_{32}(d) = -0.8d_{32} - 0.5d_{12} - 0.6d_{22} + 130;$$
$$\rho_{33}(d) = -0.9d_{33} - 0.7d_{13} - 0.5d_{23} + 133.$$

Table 5.2 displays the arc multipliers, the total operational and the total discarding cost functions with regards to the existing links as well as the new links. The computed values of the equilibrium link flows are given in Table 5.2.

The equilibrium product flows of Firms 1 and 2 on links 1 through 40 are identical to the corresponding values in Case I. When the new product produced by Firm 3 is just introduced, the manufacturers of the two existing products will not experience an immediate impact on their respective demands of branded drugs. Consequently, the equilibrium computed demands for the products of Firms 1 and 2 at the demand markets will remain as in Case I. However, the equilibrium amounts of demand for the new product of Firm 3 at each demand market is equal to:

$$d_{31}^* = 5.17, \quad d_{32}^* = 3.18, \quad \text{and } d_{33}^* = 3.01.$$

Furthermore, under the above assumptions, the equilibrium prices associated with the branded drugs 1 and 2 at the demand markets will not change, whereas the incurred equilibrium prices of generic drug 3 are as follows:

$$\rho_{31}(d^*) = 133.02, \quad \rho_{32}(d^*) = 120.30, \quad \text{and } \rho_{33}(d^*) = 123.55,$$

which is significantly lower than the respective prices of its competitors in all the demand markets. Thus, the profit that Firm 3 derived from manufacturing and delivering the new generic substitute to these 3 markets is:

$$U_3(X^*) = 637.38,$$

while the profits of Firms 1 and 2 remain unchanged. In the next case, the situation in which the consumers are now more aware of the new generic substitute of cholesterol regulators is investigated.

Table 5.2. Link Multipliers, Total Operational Cost, and Total Discarding Cost Functions and Equilibrium Link Flow Solution for Case II

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	f_a^*
1	.95	$5f_1^2 + 8f_1$	$.5f_1^2$	13.73
2	.97	$7f_2^2 + 3f_2$	$.4f_2^2$	10.77
3	.96	$6.5f_3^2 + 4f_3$	$.3f_3^2$	8.42
4	.98	$5f_4^2 + 7f_4$	$.35f_4^2$	10.55
5	1.00	$.7f_5^2 + f_5$	$.5f_5^2$	5.21
6	.99	$.9f_6^2 + 2f_6$	$.5f_6^2$	3.36
7	1.00	$.5f_7^2 + f_7$	$.5f_7^2$	4.47
8	.99	$f_8^2 + 2f_8$	$.6f_8^2$	3.02
9	1.00	$.7f_9^2 + 3f_9$	$.6f_9^2$	3.92
10	1.00	$.6f_{10}^2 + 1.5f_{10}$	$.6f_{10}^2$	3.50
11	.99	$.8f_{11}^2 + 2f_{11}$	$.4f_{11}^2$	3.10
12	.99	$.8f_{12}^2 + 5f_{12}$	$.4f_{12}^2$	2.36
13	.98	$.9f_{13}^2 + 4f_{13}$	$.4f_{13}^2$	2.63
14	1.00	$.8f_{14}^2 + 2f_{14}$	$.5f_{14}^2$	3.79
15	.99	$.9f_{15}^2 + 3f_{15}$	$.5f_{15}^2$	3.12
16	1.00	$1.1f_{16}^2 + 3f_{16}$	$.6f_{16}^2$	3.43
17	.98	$2f_{17}^2 + 3f_{17}$	$.45f_{17}^2$	8.20
18	.99	$2.5f_{18}^2 + f_{18}$	$.55f_{18}^2$	7.25
19	.98	$2.4f_{19}^2 + 1.5f_{19}$	$.5f_{19}^2$	7.97
20	.98	$1.8f_{20}^2 + 3f_{20}$	$.3f_{20}^2$	6.85
21	.98	$2.1f_{21}^2 + 3f_{21}$	$.35f_{21}^2$	5.42
22	.99	$1.9f_{22}^2 + 2.5f_{22}$	$.5f_{22}^2$	6.00
23	1.00	$.5f_{23}^2 + 2f_{23}$	$.6f_{23}^2$	3.56
24	1.00	$.7f_{24}^2 + f_{24}$	$.6f_{24}^2$	1.66
25	.99	$.5f_{25}^2 + .8f_{25}$	$.6f_{25}^2$	2.82
26	.99	$.6f_{26}^2 + f_{26}$	$.45f_{26}^2$	3.34
27	.99	$.7f_{27}^2 + .8f_{27}$	$.4f_{27}^2$	1.24
28	.98	$.4f_{28}^2 + .8f_{28}$	$.45f_{28}^2$	2.59
29	1.00	$.3f_{29}^2 + 3f_{29}$	$.55f_{29}^2$	3.45
30	1.00	$.75f_{30}^2 + f_{30}$	$.55f_{30}^2$	1.28
31	1.00	$.65f_{31}^2 + f_{31}$	$.55f_{31}^2$	3.09
32	.99	$.5f_{32}^2 + 2f_{32}$	$.3f_{32}^2$	2.54
33	.99	$.4f_{33}^2 + 3f_{33}$	$.3f_{33}^2$	3.43
34	1.00	$.5f_{34}^2 + 3.5f_{34}$	$.4f_{34}^2$	0.75
35	.98	$.4f_{35}^2 + 2f_{35}$	$.55f_{35}^2$	1.72
36	.98	$.3f_{36}^2 + 2.5f_{36}$	$.55f_{36}^2$	2.64
37	.99	$.55f_{37}^2 + 2f_{37}$	$.55f_{37}^2$	0.95
38	1.00	$.35f_{38}^2 + 2f_{38}$	$.4f_{38}^2$	3.47
39	1.00	$.4f_{39}^2 + 5f_{39}$	$.4f_{39}^2$	2.47
40	.98	$.55f_{40}^2 + 2f_{40}$	$.6f_{40}^2$	0.00
41	.97	$3f_{41}^2 + 12f_{41}$	$.3f_{41}^2$	6.17
42	.96	$2.7f_{42}^2 + 10f_{42}$	$.4f_{42}^2$	6.23
43	.98	$1.1f_{43}^2 + 6f_{43}$	$.45f_{43}^2$	3.23
44	.98	$.9f_{44}^2 + 5f_{44}$	$.45f_{44}^2$	2.75
45	.97	$1.3f_{45}^2 + 6f_{45}$	$.5f_{45}^2$	3.60
46	.99	$1.5f_{46}^2 + 7f_{46}$	$.55f_{46}^2$	2.38
47	.98	$1.5f_{47}^2 + 4f_{47}$	$.4f_{47}^2$	6.66
48	.98	$2.1f_{48}^2 + 6f_{48}$	$.45f_{48}^2$	5.05
49	.99	$.6f_{49}^2 + 3f_{49}$	$.55f_{49}^2$	3.79
50	1.00	$.7f_{50}^2 + 2f_{50}$	$.7f_{50}^2$	1.94
51	.98	$.6f_{51}^2 + 7f_{51}$	$.45f_{51}^2$	0.79
52	.99	$.9f_{52}^2 + 9f_{52}$	$.5f_{52}^2$	1.43
53	1.00	$.55f_{53}^2 + 6f_{53}$	$.55f_{53}^2$	1.23
54	.98	$.8f_{54}^2 + 4f_{54}$	$.5f_{54}^2$	2.28

5.2.3 Case III

In this case, the generic product of Firm 3 is now assumed to have been well established, and, thus, has affected the behavior of the consumers through the demand price functions of the relatively more recognized products of Firms 1 and 2. Hence, the demand price functions associated with the products of Firms 1 and 2 are no longer as in Cases I and II. The demand price functions of the three firms are now given by:

$$\rho_{11}(d) = -1.1d_{11} - 0.9d_{21} - 1.0d_{31} + 192;$$
$$\rho_{12}(d) = -0.9d_{12} - 0.8d_{22} - 0.7d_{32} + 166;$$
$$\rho_{13}(d) = -1.4d_{13} - 1.0d_{23} - 0.5d_{33} + 173;$$
$$\rho_{21}(d) = -1.2d_{21} - 0.7d_{11} - 0.8d_{31} + 176;$$
$$\rho_{22}(d) = -1.0d_{22} - 0.5d_{12} - 0.8d_{32} + 146;$$
$$\rho_{23}(d) = -1.5d_{23} - 0.4d_{13} - 0.7d_{33} + 164;$$
$$\rho_{31}(d) = -0.9d_{31} - 0.6d_{11} - 0.8d_{21} + 170;$$
$$\rho_{32}(d) = -0.8d_{32} - 0.5d_{12} - 0.6d_{22} + 153;$$
$$\rho_{33}(d) = -0.9d_{33} - 0.7d_{13} - 0.5d_{23} + 157.$$

The arc multipliers, the total operational and the total discarding cost functions are the same as in Case II, and the new computed equilibrium link flows are reported in Table 5.3.

Here, in order to study the discrete trajectory of path flows over the course of iterations, the computed path flow pattern for Case III is also displayed (Table 5.4). Having path flow information, in addition to the link flow pattern, is illuminating for the decision-makers. One can immediately realize from table 5.4 that Firm 2 chooses not to supply to demand market 2 since all of the paths belonging to O/D pair $(2, R_2)$ have zero flows.

Table 5.3. Link Multipliers, Total Operational Cost, and Total Discarding Cost Functions and Equilibrium Link Flow Solution for Case III

Link a	α_a	$\hat{c}_a(f_a)$	$\hat{z}_a(f_a)$	f_a^*
1	.95	$5f_1^2 + 8f_1$	$.5f_1^2$	8.42
2	.97	$7f_2^2 + 3f_2$	$.4f_2^2$	6.72
3	.96	$6.5f_3^2 + 4f_3$	$.3f_3^2$	6.42
4	.98	$5f_4^2 + 7f_4$	$.35f_4^2$	8.01
5	1.00	$.7f_5^2 + f_5$	$.5f_5^2$	3.20
6	.99	$.9f_6^2 + 2f_6$	$.5f_6^2$	2.07
7	1.00	$.5f_7^2 + f_7$	$.5f_7^2$	2.73
8	.99	$f_8^2 + 2f_8$	$.6f_8^2$	1.85
9	1.00	$.7f_9^2 + 3f_9$	$.6f_9^2$	2.44
10	1.00	$.6f_{10}^2 + 1.5f_{10}$	$.6f_{10}^2$	2.23
11	.99	$.8f_{11}^2 + 2f_{11}$	$.4f_{11}^2$	2.42
12	.99	$.8f_{12}^2 + 5f_{12}$	$.4f_{12}^2$	1.75
13	.98	$.9f_{13}^2 + 4f_{13}$	$.4f_{13}^2$	2.00
14	1.00	$.8f_{14}^2 + 2f_{14}$	$.5f_{14}^2$	2.84
15	.99	$.9f_{15}^2 + 3f_{15}$	$.5f_{15}^2$	2.40
16	1.00	$1.1f_{16}^2 + 3f_{16}$	$.6f_{16}^2$	2.60
17	.98	$2f_{17}^2 + 3f_{17}$	$.45f_{17}^2$	5.02
18	.99	$2.5f_{18}^2 + f_{18}$	$.55f_{18}^2$	4.49
19	.98	$2.4f_{19}^2 + 1.5f_{19}$	$.5f_{19}^2$	4.96
20	.98	$1.8f_{20}^2 + 3f_{20}$	$.3f_{20}^2$	5.23
21	.98	$2.1f_{21}^2 + 3f_{21}$	$.35f_{21}^2$	4.11
22	.99	$1.9f_{22}^2 + 2.5f_{22}$	$.5f_{22}^2$	4.56
23	1.00	$.5f_{23}^2 + 2f_{23}$	$.6f_{23}^2$	2.44
24	1.00	$.7f_{24}^2 + f_{24}$	$.6f_{24}^2$	1.47
25	.99	$.5f_{25}^2 + .8f_{25}$	$.6f_{25}^2$	1.02
26	.99	$.6f_{26}^2 + f_{26}$	$.45f_{26}^2$	2.48
27	.99	$.7f_{27}^2 + .8f_{27}$	$.4f_{27}^2$	1.31
28	.98	$.4f_{28}^2 + .8f_{28}$	$.45f_{28}^2$	0.66
29	1.00	$.3f_{29}^2 + 3f_{29}$	$.55f_{29}^2$	2.29
30	1.00	$.75f_{30}^2 + f_{30}$	$.55f_{30}^2$	1.29
31	1.00	$.65f_{31}^2 + f_{31}$	$.55f_{31}^2$	1.28
32	.99	$.5f_{32}^2 + 2f_{32}$	$.3f_{32}^2$	2.74
33	.99	$.4f_{33}^2 + 3f_{33}$	$.3f_{33}^2$	0.00
34	1.00	$.5f_{34}^2 + 3.5f_{34}$	$.4f_{34}^2$	2.39
35	.98	$.4f_{35}^2 + 2f_{35}$	$.55f_{35}^2$	1.82
36	.98	$.3f_{36}^2 + 2.5f_{36}$	$.55f_{36}^2$	0.00
37	.99	$.55f_{37}^2 + 2f_{37}$	$.55f_{37}^2$	2.21
38	1.00	$.35f_{38}^2 + 2f_{38}$	$.4f_{38}^2$	3.46
39	1.00	$.4f_{39}^2 + 5f_{39}$	$.4f_{39}^2$	0.00
40	.98	$.55f_{40}^2 + 2f_{40}$	$.6f_{40}^2$	1.05
41	.97	$3f_{41}^2 + 12f_{41}$	$.3f_{41}^2$	8.08
42	.96	$2.7f_{42}^2 + 10f_{42}$	$.4f_{42}^2$	8.13
43	.98	$1.1f_{43}^2 + 6f_{43}$	$.45f_{43}^2$	4.21
44	.98	$.9f_{44}^2 + 5f_{44}$	$.45f_{44}^2$	3.63
45	.97	$1.3f_{45}^2 + 6f_{45}$	$.5f_{45}^2$	4.62
46	.99	$1.5f_{46}^2 + 7f_{46}$	$.55f_{46}^2$	3.19
47	.98	$1.5f_{47}^2 + 4f_{47}$	$.4f_{47}^2$	8.60
48	.98	$2.1f_{48}^2 + 6f_{48}$	$.45f_{48}^2$	6.72
49	.99	$.6f_{49}^2 + 3f_{49}$	$.55f_{49}^2$	3.63
50	1.00	$.7f_{50}^2 + 2f_{50}$	$.7f_{50}^2$	3.39
51	.98	$.6f_{51}^2 + 7f_{51}$	$.45f_{51}^2$	1.41
52	.99	$.9f_{52}^2 + 9f_{52}$	$.5f_{52}^2$	1.12
53	1.00	$.55f_{53}^2 + 6f_{53}$	$.55f_{53}^2$	2.86
54	.98	$.8f_{54}^2 + 4f_{54}$	$.5f_{54}^2$	2.60

Table 5.4. Paths Definition and Optimal Path Flow Pattern for Case III

	Path Definition	Path Flow
O/D Pair $(1, R_1)$	$p_1 = (1, 5, 17, 23)$	$x^*_{p_1} = 1.87$
	$p_2 = (1, 6, 18, 26)$	$x^*_{p_2} = 1.46$
	$p_3 = (1, 7, 19, 29)$	$x^*_{p_3} = 1.57$
	$p_4 = (2, 8, 17, 23)$	$x^*_{p_4} = 0.73$
	$p_5 = (2, 9, 18, 26)$	$x^*_{p_5} = 1.17$
	$p_6 = (2, 10, 19, 29)$	$x^*_{p_6} = 0.87$
O/D Pair $(1, R_2)$	$p_7 = (1, 5, 17, 24)$	$x^*_{p_7} = 0.89$
	$p_8 = (1, 6, 18, 27)$	$x^*_{p_8} = 0.57$
	$p_9 = (1, 7, 19, 30)$	$x^*_{p_9} = 0.66$
	$p_{10} = (2, 8, 17, 24)$	$x^*_{p_{10}} = 0.68$
	$p_{11} = (2, 9, 18, 27)$	$x^*_{p_{11}} = 0.82$
	$p_{12} = (2, 10, 19, 30)$	$x^*_{p_{12}} = 0.71$
O/D Pair $(1, R_3)$	$p_{13} = (1, 5, 17, 25)$	$x^*_{p_{13}} = 0.60$
	$p_{14} = (1, 6, 18, 28)$	$x^*_{p_{14}} = 0.16$
	$p_{15} = (1, 7, 19, 31)$	$x^*_{p_{15}} = 0.64$
	$p_{16} = (2, 8, 17, 25)$	$x^*_{p_{16}} = 0.49$
	$p_{17} = (2, 9, 18, 28)$	$x^*_{p_{17}} = 0.53$
	$p_{18} = (2, 10, 19, 31)$	$x^*_{p_{18}} = 0.72$
O/D Pair $(2, R_1)$	$p_{19} = (3, 11, 20, 32)$	$x^*_{p_{19}} = 1.26$
	$p_{20} = (3, 12, 21, 35)$	$x^*_{p_{20}} = 0.77$
	$p_{21} = (3, 13, 22, 38)$	$x^*_{p_{21}} = 1.51$
	$p_{22} = (4, 14, 20, 32)$	$x^*_{p_{22}} = 1.63$
	$p_{23} = (4, 15, 21, 35)$	$x^*_{p_{23}} = 1.16$
	$p_{24} = (4, 16, 22, 38)$	$x^*_{p_{24}} = 2.12$
O/D Pair $(2, R_2)$	$p_{25} = (3, 11, 20, 33)$	$x^*_{p_{25}} = 0.00$
	$p_{26} = (3, 12, 21, 36)$	$x^*_{p_{26}} = 0.00$
	$p_{27} = (3, 13, 22, 39)$	$x^*_{p_{27}} = 0.00$
	$p_{28} = (4, 14, 20, 33)$	$x^*_{p_{28}} = 0.00$
	$p_{29} = (4, 15, 21, 36)$	$x^*_{p_{29}} = 0.00$
	$p_{30} = (4, 16, 22, 39)$	$x^*_{p_{30}} = 0.00$
O/D Pair $(2, R_3)$	$p_{31} = (3, 11, 20, 34)$	$x^*_{p_{31}} = 1.26$
	$p_{32} = (3, 12, 21, 37)$	$x^*_{p_{32}} = 1.05$
	$p_{33} = (3, 13, 22, 40)$	$x^*_{p_{33}} = 0.57$
	$p_{34} = (4, 14, 20, 34)$	$x^*_{p_{34}} = 1.26$
	$p_{35} = (4, 15, 21, 37)$	$x^*_{p_{35}} = 1.29$
	$p_{36} = (4, 16, 22, 40)$	$x^*_{p_{36}} = 0.54$
O/D Pair $(3, R_1)$	$p_{37} = (41, 43, 47, 49)$	$x^*_{p_{37}} = 1.87$
	$p_{38} = (41, 44, 48, 52)$	$x^*_{p_{38}} = 1.78$
	$p_{39} = (42, 45, 47, 49)$	$x^*_{p_{39}} = 0.70$
	$p_{40} = (42, 46, 48, 52)$	$x^*_{p_{40}} = 0.68$
O/D Pair $(3, R_2)$	$p_{41} = (41, 43, 47, 50)$	$x^*_{p_{41}} = 1.61$
	$p_{42} = (41, 44, 48, 53)$	$x^*_{p_{42}} = 1.46$
	$p_{43} = (42, 45, 47, 50)$	$x^*_{p_{43}} = 2.07$
	$p_{44} = (42, 46, 48, 53)$	$x^*_{p_{44}} = 1.90$
O/D Pair $(3, R_3)$	$p_{45} = (41, 43, 47, 51)$	$x^*_{p_{45}} = 0.84$
	$p_{46} = (41, 44, 48, 54)$	$x^*_{p_{46}} = 0.53$
	$p_{47} = (42, 45, 47, 51)$	$x^*_{p_{47}} = 1.46$
	$p_{48} = (42, 46, 48, 54)$	$x^*_{p_{48}} = 1.33$

The computed equilibrium demands for the products of Firms 1, 2, and 3 are as follows:

$$d_{11}^* = 7.18, \quad d_{12}^* = 4.06, \quad d_{13}^* = 2.93,$$
$$d_{21}^* = 7.96, \quad d_{22}^* = 0.00, \quad d_{23}^* = 5.60,$$
$$d_{31}^* = 4.70, \quad d_{32}^* = 6.25, \quad d_{33}^* = 3.93.$$

As a result of the consumers' growing inclination towards the generic substitute of the previously popular Lipitor, the link flow and the demand pattern has now significantly changed. For example, Firm 2 has lost its entire share of market 2 to its competitors, resulting in zero flows on the corresponding distribution links: 33, 36, and 39. Similarly, Firm 1 now has declining sales of its brand in demand markets 1 and 3. As noted by Johnson (2011), the market share of a branded drug may decrease by as much as 40%–80% after the introduction of its generic rival. Thus, the model captures the observed decrease in the US market share.

Furthermore, as expected, the introduction of the generic substitute of cholesterol regulators has also caused remarkable drops in the prices of the existing brands. Interestingly, the decrease in the price of Firm 1's product – Lipitor – in demand markets 2 and 3 exceeds 35%:

$$\rho_{11}(d^*) = 172.24, \quad \rho_{12}(d^*) = 157.97, \quad \rho_{13}(d^*) = 161.33,$$
$$\rho_{21}(d^*) = 157.66, \quad \rho_{22}(d^*) = 138.97, \quad \rho_{23}(d^*) = 151.67,$$
$$\rho_{31}(d^*) = 155.09, \quad \rho_{32}(d^*) = 145.97, \quad \rho_{33}(d^*) = 148.61.$$

Finally, the computed amounts of profit for each of the three competitors through the production and delivery of their respective cholesterol-lowering medicines are as follows:

$$U_1(X^*) = 1,199.87, \quad U_2(X^*) = 1,062.73, \quad \text{and } U_3(X^*) = 980.83.$$

Note that simultaneous declines in the amounts of demand and sales price has caused a severe reduction in the profits of Firms 1 and 2. This decline for Firm 1

is observed to be as high as 60%. The reduction in demand and price due to the patent expiration has been observed in the market sales. The US sales of Lipitor have dropped over 75% (Forbes (2012) and Fiercepharma (2012)).

5.3. Graphical Presentation of the Solution Iterates Trajectories

In this section, additional results for Case III are presented. Note that for the convergence tolerance of 10^{-6}, the Euler method required 33 iterations to yield the equilibrium solution for Case III.

Figures 5.5-5.12 provide the graphical depiction of the iterates, consisting of the pharmaceutical products' path flows. In each of these figures, the computed stationary/equilibrium values of the path flows are exactly equal to the respective values reported in Table 5.4.

For example, look at Figure 5.9, which displays the product flow iterates on paths connecting Firm 2 to market 2. After only 9 iterations, all flows on paths p25–p30 have converged to zero. That is the case where in Case III, Firm 2 loses its entire share of market 2 to Firms 1 and 3 – as noted in Table 5.4. Also, for all other paths the convergence is relatively fast.

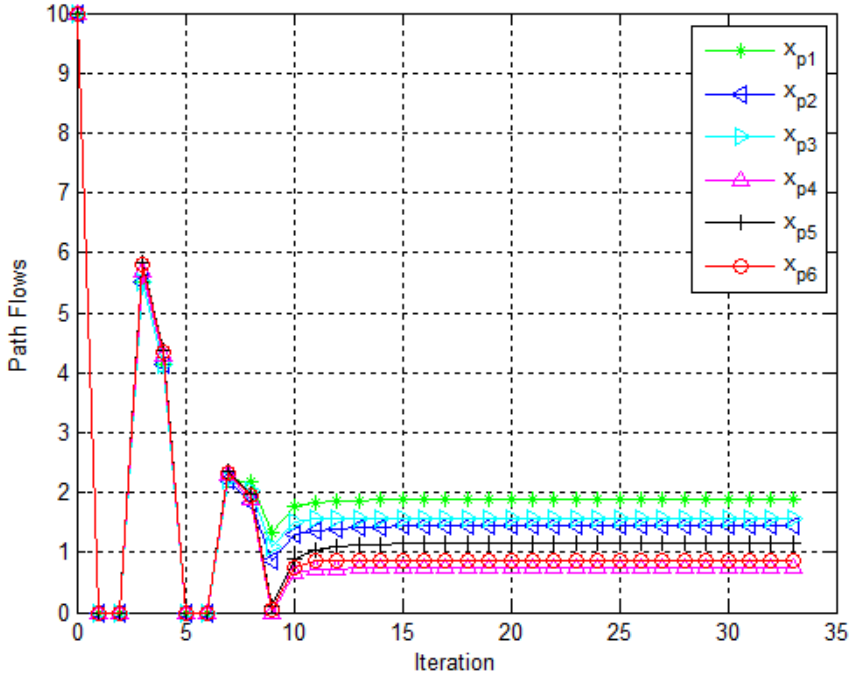

Figure 5.5. The Trajectories of Product Flows on Paths $p_1 - p_6$ for Case III

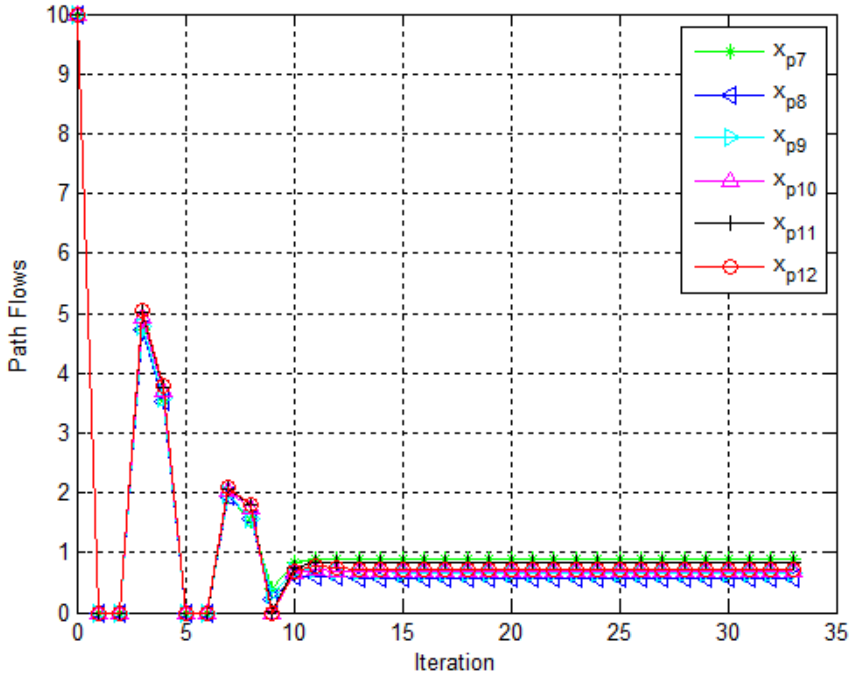

Figure 5.6. The Trajectories of Product Flows on Paths $p_7 - p_{12}$ for Case III

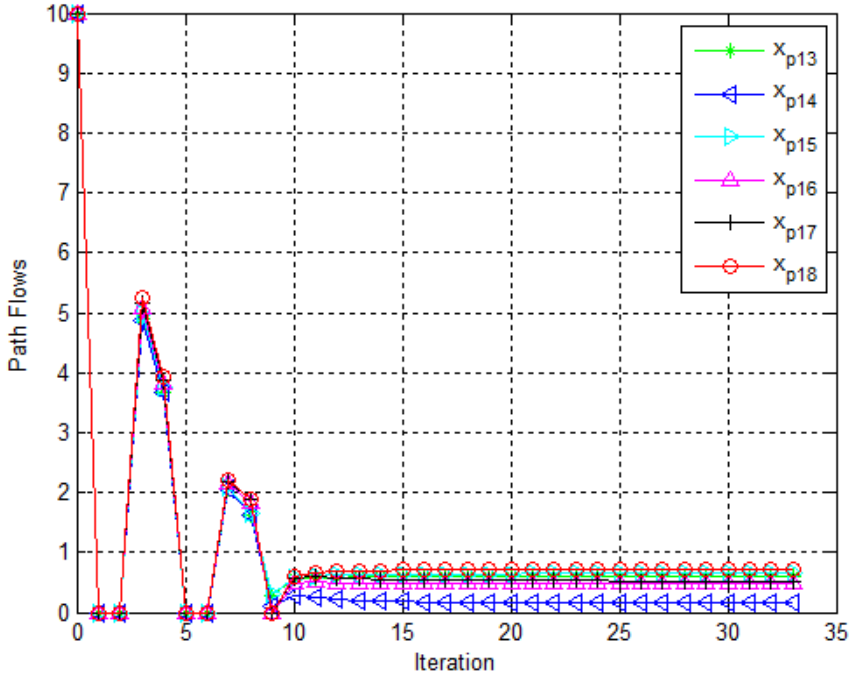

Figure 5.7. The Trajectories of Product Flows on Paths $p_{13} - p_{18}$ for Case III

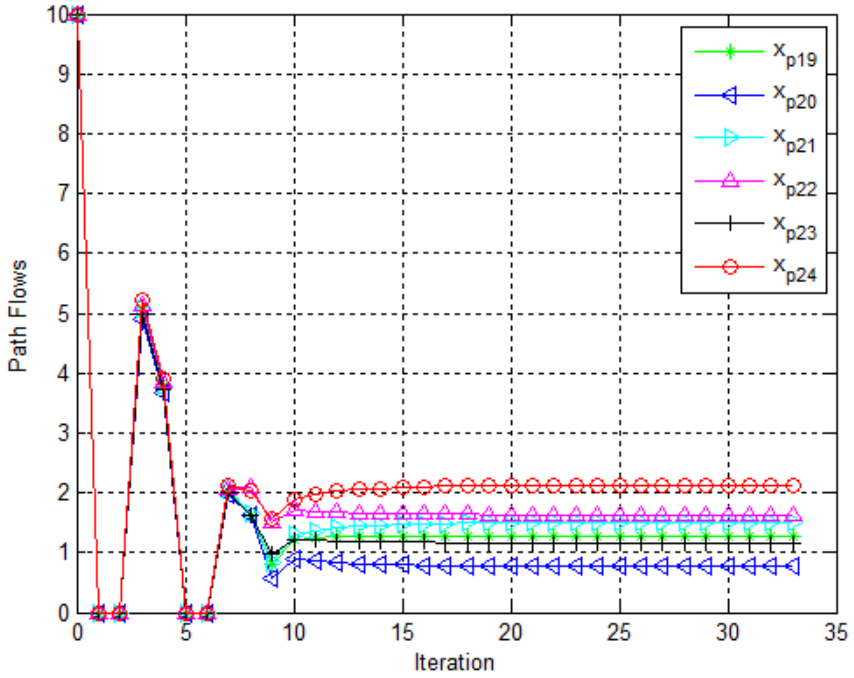

Figure 5.8. The Trajectories of Product Flows on Paths $p_{19} - p_{24}$ for Case III

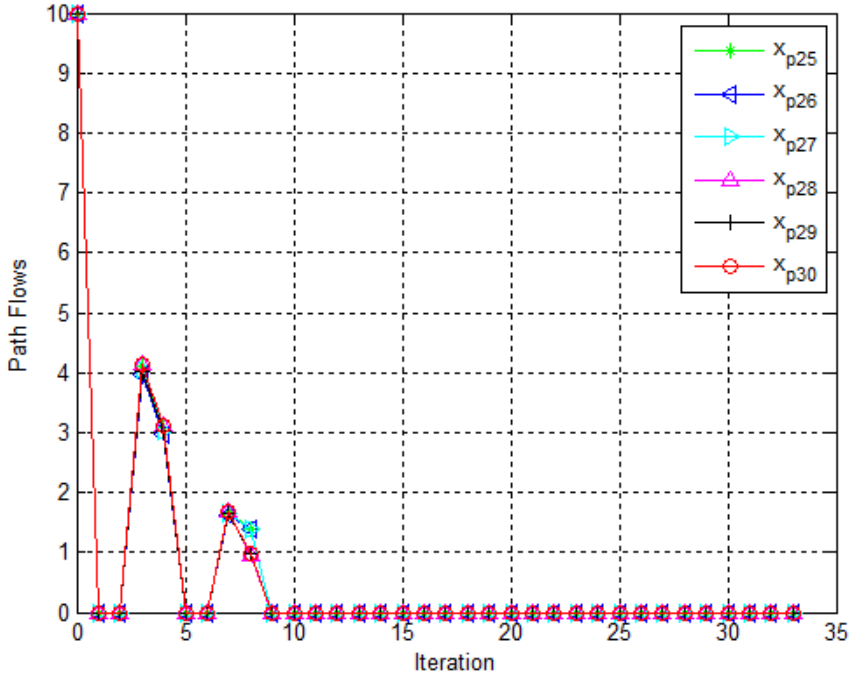

Figure 5.9. The Trajectories of Product Flows on Paths $p_{25} - p_{30}$ for Case III

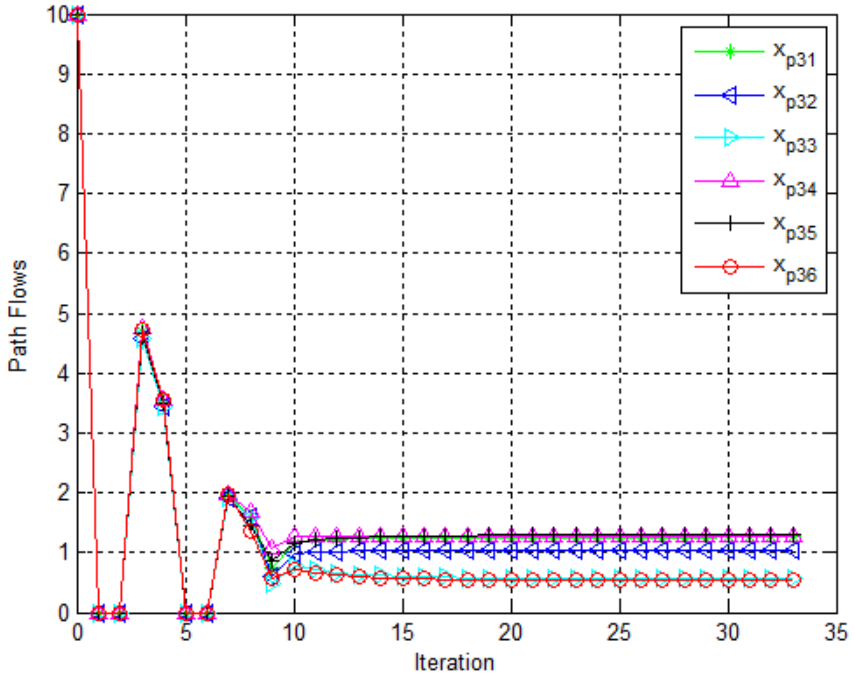

Figure 5.10. The Trajectories of Product Flows on Paths $p_{31} - p_{36}$ for Case III

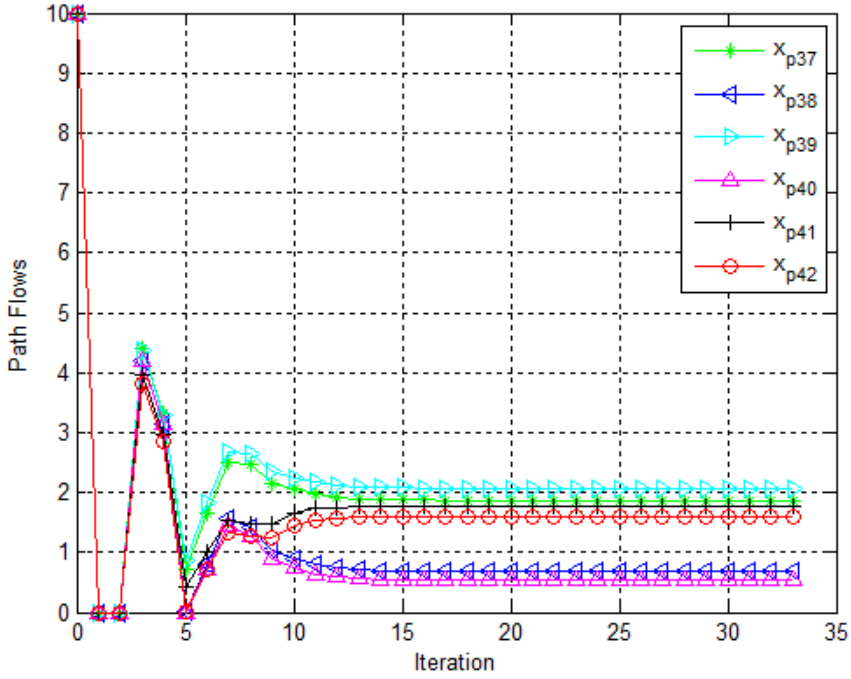

Figure 5.11. The Trajectories of Product Flows on Paths $p_{37} - p_{42}$ for Case III

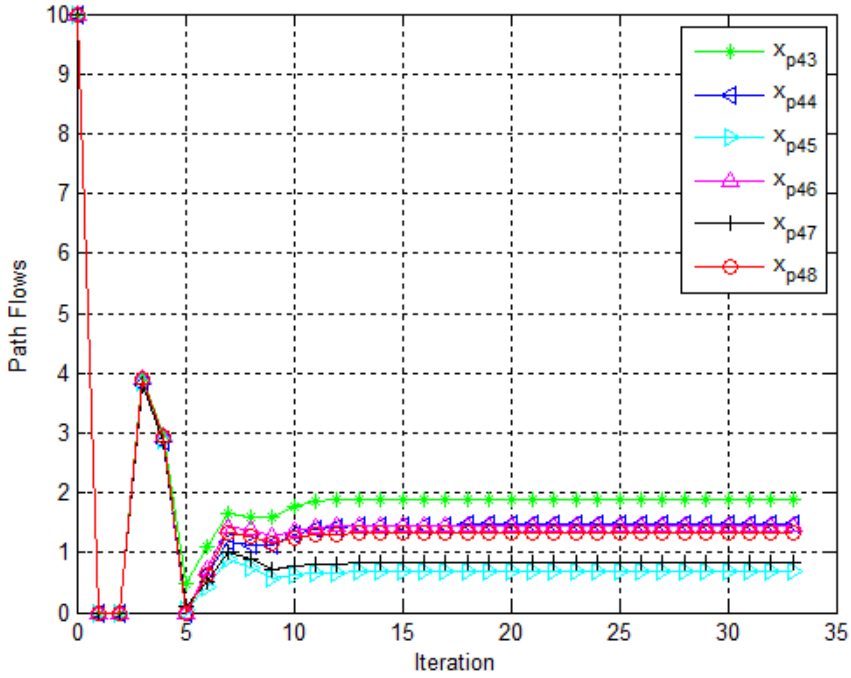

Figure 5.12. The Trajectories of Product Flows on Paths $p_{43} - p_{48}$ for Case III

5.4. Summary and Conclusions

In this chapter, a supply chain network model was developed for the study of oligopolistic competition among the producers of a perishable product – that of medication drugs. The supply chain of each pharmaceutical company consists of activities of manufacturing, shipment, storage, and the ultimate distribution to the demand markets. The model has several novel features, described below.

It captures the perishability of pharmaceuticals through the use of arc multipliers; it assesses the discarding cost associated with the disposal of waste/perished products in the supply chain network activities; it investigates the oligopolistic competition among the supply chains of pharmaceutical industry firms; it handles product differentiation by the consumers, capturing, for example, as to whether or not the products are branded or generic; and, its solution yields the equilibrium values of the product demands and the incurred product prices as well as of the product path and link flows.

Special cases of the model were also established in order to reflect situations and applications in which the drugs are homogeneous or the demands for the product remain differentiated but are known and fixed, rather than elastic. Subsequently, the model was illustrated through a case study consisting of several numerical examples including the interesting scenario of the substitution of a highly popular branded drug by a generic one, as a result of the patent rights expiration of the brand. The observations form the real-world problem – including declining sales and profit for the manufacturer of formerly popular brands – confirm our calculated results for such impacts.

For the sake of generality, and to enable further extensions and applications, a variational inequality approach was used for model formulation, analysis, and solution. In addition, a projected dynamical system (PDS) version of the problem was derived.

The proposed model of network competition for pharmaceutical supply chains can also be applied to other oligopolies of perishable products, albeit after appropriate modifications (e.g., Yu and Nagurney (2013)).

CHAPTER 6

CONCLUSIONS AND FUTURE RESEARCH

Over the past few years, the economic situation has affected organizations and companies worldwide. That, and globalization have mandated the effective management of supply chain networks. When it comes to the supply chains of healthcare products and services, various aspects of safety and health also play critical roles. Among healthcare products, those with a high tendency to perish, impose unique challenges to decision-makers in such industries.

The purpose of this dissertation was to contribute to the analysis, management, design, and redesign of supply chains of perishable healthcare products with a focus on human blood and pharmaceuticals.

In Chapters 3 and 4, healthcare supply chains operating under centralized decision-making behavior were studied. More specifically, a mathematical framework for the supply chain network of a blood bank was developed. The focus was on the case of a regional blood bank, as belonging to the American Red Cross. Since almost all other blood banks have more or less the same structure, the proposed framework can simply be applied to blood banks across the globe.

In Chapter 3, the operations management network optimization problem of a blood bank was formulated. Through the introduction of generalized arc multipliers, I derived the optimization formulation that determined the optimal level of activities on every link in the network. That included the optimization of the flow of whole blood or red blood cells over various links/activities of blood collection, transportation, testing and processing, storage, and distribution. The problem was formulated

as a weighted-sum multicriteria optimization model where the two criteria were the minimization of total cost as well as the minimization of supply-side risk. Total cost, in turn, consisted of total operational cost in addition to the total discarding cost of outdated/wasted units of blood. The risk, on the other hand, represented variations on blood collection links originating from inclement weather conditions, donors' inability to make their appointments, etc. The demand at the demand points was assumed to be uncertain where shortage and surplus penalties captured excess demand or excess supply at the hospitals and other demand points. The optimization formulation was then reexpressed in terms of its equivalent variational inequality problem that provided nice features for computation. Numerical examples were also provided and sensitivity analysis was conducted. Thus, the balance between the shortage versus the outdating of product through the manipulation of shortage penalties and the perishability ratio was investigated.

Chapter 4 discussed another case of centralized (system-optimization) decision-making behavior where the objective was to design/redesign a regional blood banking system. The objective function incorporated the minimization of total cost and total supply side-risk while the uncertain demand was satisfied as closely as possible. The total cost criterion consisted of an additional element as compared to that of Chapter 3 – the total investment cost pertaining to the capacity adjustments. The solution to the optimization problem not only provided the optimal levels of link activities, but also determined the optimal enhancement/reduction in the capacities of all network activities as well the corresponding shadow prices. The proposed model also identified the links (activities) and nodes (facilities) that possibly needed to be shut down in order to minimize the total cost and risk. This analysis is quite timely, and is of critical importance since the American Red Cross has been restructuring its blood services through the closure of several of its blood centers and testing labs as a part of a five year plan to eliminate its $209 million annual operating deficit (Rios (2010)

and Hunt (2012)). The model was referred to as "sustainable network design" in that the optimal design also resulted in the minimization of total discarding cost of waste. Note that shuttering unnecessary activities of blood supply chains can lead to a more sustainable system via significant savings.

In Chapter 5, the case of decentralized decision-making behavior for supply chains was taken into consideration. The focus was on another perishable product – that of pharmaceuticals. In contrast to the Chapters 3 and 4, where a single organization was in charge of its entire network of facilities, here, a network oligopoly model was developed to capture the competition among supply chains of multiple pharmaceutical firms. Through product differentiation, the customers' willingness to buy a specific brand as a result of difference in price, perceived quality, etc. was captured.

The developed model for pharmaceutical oligopoly also enabled addressing one major challenge in this industry: the expiration of patent rights of specific brands and its impact on the demand markets. Using a case study based on real-world scenarios of the most popular brand of cholesterol-reducing drugs, the situation of demand markets before, a few weeks after, and several months after the expiration of patent rights of that brand was explored. The patent expiration of a branded drug typically coincides with its generic substitutes' entering the markets which leads to enormous declines in price, sales and profit for the manufacturer of that brand. Comparison of the actual observations of the market with that of my calculated predictions indicated similar impacts on the demand market under such conditions. Finally, a projected dynamical system (PDS) model of the dynamic network oligopoly problem for pharmaceutical supply chains was constructed.

6.1. Future Research

The network optimization models presented in Chapters 3 and 4 of this dissertation – corresponding to the operations management and the sustainable design of

a blood bank, respectively – captured the aspect of perishability/waste/loss through the use of generalized arc multipliers. In other words, the multipliers represented the percentage of throughput during various activities of blood banking. On the other hand, due to the assumption of demand uncertainty, assigning surplus penalties to the demand points addressed the outdating of products resulting from unused units of blood at the end of the planning horizon of the problem.

While this model addresses such aspects as waste and the outdating of blood, it is not meant to tackle the inventory management problem of perishable products. Specifically, for the case of fixed lifetime perishable goods, a multiperiod inventory management with explicit time elements can be developed. As an extension to the existing model, I plan to develop a multiperiod supply chain operations management of blood banks that allows for the incorporation of inputs (newly arrived units) and outputs (outdated/expired units) at every period of the planning horizon.

Another topic related to the area of blood banking is the practicality of mathematical supply chain methods. In today's blood banks, the determination of optimal levels of activities as well as optimal capacities on links are largely done based on historical data. As an extension to the models in Chapters 3 and 4 of this dissertation, I would like to conduct a feasibility test to adapt/apply the proposed mathematical framework for blood banks at the regional level. That, of course, requires access to sufficient data resources by the decision-makers. Also, a cost-benefit analysis has to be conducted in advance to predict the short-term versus long-term impacts of implementation of the calculated results. I also plan to conduct empirical research in the area of blood banking systems. The insights from this work will assist with the understanding of the challenges associated with this critical component of the healthcare system.

In Chapter 5, a network model for the case of pharmaceutical firms in a competitive oligopolistic market under brand differentiation was developed. Today, pharma-

ceutical firms have increasingly adopted outsourcing as a strategic weapon to confront issues such as rising costs and declining R&D productivity (Higgins and Rodriguez (2006) and Enyinda, Briggs, and Bachkar (2009)). I plan to study the possibility of outsourcing various activities of pharmaceutical firms including innovation, manufacturing, and distribution. Analyzing the impact of such outsourcing options on customers' willingness can be a rigorous extension to the model developed in Chapter 5 of this dissertation.

Nonetheless, fragmentation of such processes incurs various types of risks to the pharmaceutical firms ranging from operational risks to technical risk to corporate social responsibility risk (Enyinda, Briggs, and Bachkar (2009) and Lowman et al. (2012)). Recalling a pharmaceutical brand as a result of distributing unsafe or contaminated product to the market is not a rare event. The impact of such recalls on the competitive market, and the firms' potential preventive efforts to enhance the quality assurance of their products can also be further investigated.

A completely different application of healthcare products that I plan to conduct research on is humanitarian logistics, in general, and disaster relief supply chains, in particular.

The number of natural disasters and the number of claimed lives worldwide due to these disasters have been growing (Schultz, Koenig, and Noji (1996), Nagurney and Qiang (2009), and Sheppard (2011)). Furthermore, scientists have warned that we should expect cases of extreme events even more often in the future. Nevertheless, research on disaster relief supply chains has been limited (Day, Junglas, and Silva (2009)).

Disasters are often unavoidable and unpredictable, and, consequently, supply chain management is seldom considered to be more difficult than during disaster relief efforts (Day, Junglas, and Silva (2009)). The complexity of disaster relief supply chains originates from several inherent factors. First of all, the associated large

demands pose challenges to the logistics planning authorities (Lin (2010)). What adds to the complexity is the level of uncertainty. According to Beamon and Kotleba (2006), there may exist unique irregularities in size, timing, and location of relief goods demand patterns.

In addition, disaster-driven supply chains are, typically, formed as incident-responsive ones with temporary configurations of disparate resources. Commercial supply chains often evolve supplier-buyer relationships over the course of years or decades along with the refinement of policies and fulfillment of investments. In contrast, disaster relief systems develop new networks of relationships within days or even hours, and have very short life-cycles (Oloruntoba and Gray (2006) and Denning (2006)).

Thus, "time" plays an extremely critical role in the construction and operation of such networks. As noted by Tzeng, Cheng, and Huang (2007), once a disaster such as an earthquake strikes, effective disaster salvaging efforts can mitigate the damage, reduce the number of fatalities, and bring relief to surviving victims.

I plan to construct an integrated supply chain model corresponding to a humanitarian organization in charge of procurement and distribution of disaster relief items to the affected areas. The model should incorporate explicit time elements to ensure timely delivery of relief goods subject to the uncertain demand being satisfied as closely as possible. As an extension to such a model, the performance of centralized (system-optimized) vs. decentralized (distributed) supply chains for the distribution of disaster relief items can be compared. In addition, the scenarios of short-term teaming of disaster relief organizations can be investigated with the purpose of enhancing the effectiveness of relief delivery while minimizing the total costs. Nagurney (2009) and (2010c), Nagurney and Woolley (2010), and Liu and Nagurney (2011b) have developed mergers and acquisition models. The humanitarian organizations involved with the procurement and distribution of relief goods will not be of profit-

maximizing status. In addition, perishability of certain disaster relief goods can be taken into consideration.

BIBLIOGRAPHY

Abad, P., 1996. Optimal pricing and lot-sizing under conditions of perishability and partial backordering. *Management Science* 42, 1093–1104.

Ahumada, O., Villalobos, J., 2009. Application of planning models in the agri-food supply chain: A review. *European Journal of Operational Research* 195, 1–20.

Alshawi, S., Missi, F., Eldabi, T., 2003. Healthcare information management: The integration of patients data. *Logistics Information Management* 16(3/4), 286–295.

Amaro, A., Barbosa-Povoa, A., 2008. Planning and scheduling of industrial supply chains with reverse flows: A real pharmaceutical case study. *Computers & Chemical Engineering* 32(11), 2606–2625.

America's Blood Centers, 2011. 56 facts about blood.
Available online at: http://www.americasblood.org/go.cfm?do=page.view&pid=12.

Anjos, M., Cheng, R., Currie, C., 2005. Optimal pricing policies for perishable products. *European Journal of Operational Research* 166(1), 246–254.

Association of Bay Area Governments, 2003. Why are hospitals rethinking regulated medical waste management? Environmental Best Practices for Health Care Facilities – June.

Atkinson, M., Fontaine, M., Goodnough, L., Wein, L., 2012. A novel allocation strategy for blood transfusions: Investigating the tradeoff between the age and availability of transfused blood. *Transfusion* 52(1), 108–117.

Bai, R., Kendall, G., 2008. A model for fresh produce shelf space allocation and inventory management with freshness condition dependent demand. *INFORMS Journal on Computing* 20(1), 78–85.

Balasubramanian, H., Muriel, A., Wang, L., 2012. The impact of provider flexibility and capacity allocation on the performance of primary care practices. *Flexible Services and Manufacturing Journal* 24(4), 422-447.

Bazaraa, M., Sherali, H., Shetty, C., 1993. *Nonlinear programming: Theory and algorithms*, second edition. John Wiley & Sons, New York.

Beamon, B., Kotleba, S., 2006. Inventory management support systems for emergency humanitarian relief operations in South Sudan. *International Journal of Logistics Management* 17(2), 187–212.

Beckmann, M., McGuire, C., Winsten, C., 1956. *Studies in the economics of transportation*, Yale University Press, New Haven, Connecticut.

Belien, J., Force, H., 2012. Supply chain management of blood products: A literature review. *European Journal of Operational Research* 217(1), 1–16.

Ben Natan, M., Gorkov, L., 2011. Investigating the factors affecting blood donation among Israelis. *International Emergency Nursing* 19, 37-43.

Bhattacharjee, S., Ramesh, R., 2000. A multi-period profit maximizing model for retail supply chain management: An integration of demand and supply-side mechanisms. *European Journal of Operational Research* 122(3), 584–601.

Blackburn, J., Scudder, G., 2009. Supply chain strategies for perishable products: The case of fresh produce. *Production and Operations Management* 18, 129–137.

Blazona, B., Koncar, M., 2007. HL7 and DICOM based integration of radiology departments with healthcare enterprise information systems. *International Journal of Medical Informatics* 76(3), 425–432.

Boppana, R., Chalasani, S., 2007. Analytical models to determine desirable blood acquisition rates. IEEE International Conference on System of Systems Engineering.

Boulaksil, Y., 2009. Planning of outsourced operations in pharmaceutical supply chains. Ph.D. thesis in Operations Management and Logistics, The BETA Research School, Netherlands.

Breen, L., Crawford, H., 2005. Improving the pharmaceutical supply chain: Assessing the reality of e-quality through e-commerce application in hospital pharmacy. *International Journal of Quality & Reliability Management* 22(6), 572–590.

Brodheim, E., Derman, C., Prastacos, G., 1975. On the evaluation of a class of inventory policies for perishable products such as blood. *Management Science* 21(11), 1320–1325.

Burnetas, A, Smith, C., 2000. Adaptive ordering and pricing for perishable products. *Operations Research* 48(3), 436–443.

Business Wire, 2009. CVS has consumers going nuts over expired milk, eggs, infant formula, medicine, according to Change to Win. April 2.
Available online at: http://www.businesswire.com/news/google/20090402006264/en.

Cakici, O., Groenevelt, H., Seidmann, A., 2011. Using RFID for the management of pharmaceutical inventory - System optimization and shrinkage control. *Decision Support Systems* 51(4), 842-852.

Cetin, E., Sarul L., 2009. A blood bank location model: A multiobjective approach. *European Journal of Pure and Applied Mathematics* 2(1), 112–124.

Chahed, S., Marcon, E., Sahin, E., Feillet, D., Dallery, Y., 2009. Exploring new operational research opportunities within the home care context: The chemotherapy at home. *Health Care Management Science* 12, 179–191.

Chande, A., Dhekane, S., Hemachandra, N., Rangaraj, N., 2005. Perishable inventory management and dynamic pricing using RFID technology. *SADHANA* 30(2-3), 445–462.

Chatwin, R., 2000. Optimal dynamic pricing of perishable products with stochastic demand and a finite set of prices. *European Journal of Operational Research* 125(1), 149–174.

Chen, I., 2010. In a world of throwaways, making a dent in medical waste. *The New York Times*. July 5.
Available online at: http://www.nytimes.com/2010/07/06/health/06waste.html.

Christopher, M., 2005. *Logistics and supply chain management: Creating value-adding networks*, third edition. Prentice-Hall/Financial Times, London, UK.

Cohen, M., Pierskalla, W., 1979. Target inventory levels for a hospital blood bank or a decentralized regional blood banking system. *Transfusion* 19(4), 444–454.

Cohen, M., Pierskalla, W., Yen, H.-C., 1981. An analysis of ordering and allocation policies for multi-echelon, age-differentiated inventory systems. *TIMS Studies in the Management Sciences* 16, 353–378.

Cohon, J., 1978. *Multiobjective programming and planning*. Academic Press, New York.

Cournot, A., 1838. *Researches into the mathematical principles of the theory of wealth*, English translation, MacMillan, London, England.

Craighead, C., Blackhurst, J., Rungtusanatham, M., Handfield, R., 2007. The severity of supply chain disruptions: Design characteristics and mitigation capabilities. *Decision Sciences* 38(1), 131–156.

Dafermos, S., 1971. An extended traffic assignment model with applications to two-way traffic. *Transportation Science* 5, 366-389.

Dafermos, S., Nagurney, A., 1987. Oligopolistic and competitive behavior of spatially separated markets. *Regional Science and Urban Economics* 17, 245–254.

Dafermos, S., Sparrow, F., 1969. The traffic assignment problem for a general network. *Journal of Research of the National Bureau of Standards* 73B, 91–118.

Day, J., Junglas, I., Silva, L., 2009. Information flow impediments in disaster relief supply chains. *Journal of the Association for Information Systems* 10(8), 637–660.

De la Garza, D., 2011. Pharmaceutical patent protection and why 2012 is the year companies fear the most. *The Strategic Sourceror*. September 1.
Available online at: http://www.strategicsourceror.com/2011/09/pharmaceutical-patent-protection-and.html.

Denning, P., 2006. Hastily formed networks. *Communications of the ACM* 49(4), 15–20.

Dong, J., Zhang, D., Nagurney, A., 2004. A supply chain network equilibrium model with random demands. *European Journal of Operational Research* 156, 194–212.

Dunehew, A., 2005. Changing dynamics in the pharmaceutical supply chains: A GPO perspective. *American Journal of Health-System Pharmacy* 62, 527–529.

Dupuis, P., Nagurney, A., 1993. Dynamical systems and variational inequalities. *Annals of Operations Research* 44, 9–42.

Emanuel, E., 2011. Shortchanging cancer patients. *The New York Times*. August 6.
Available online at: http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html.

Entrup, M., 2005. Advanced planning in fresh food industries: Integrating shelf life into production planning. Physica-Verlag, Heidelberg, Germany.

Enyinda, C., 2008. Modeling risk management in the pharmaceutical industry global supply chain logistics using analytic hierarchy process model. Ph.D. thesis, North Dakota State University, Fargo, North Dakota.

Enyinda, C., Briggs, C., Bachkar, K., 2009. Managing risk in pharmaceutical global supply chain outsourcing: Applying analytic hierarchy process model. Proceedings of American Society of Business and Behavioral Sciences (ASBBS) Annual Conference 16(1), Las Vegas, Nevada.

Federgruen, A., Prastacos, G., Zipkin, P., 1986. An allocation and distribution model for perishable products. *Operations Research* 34(1), 75–82.

Feng, Y., Xiao, B., 2006. Integration of pricing and capacity allocation for perishable products. *European Journal of Operational Research* 168(1), 17–34.

Fiercepharma, 2012. Lipitor copy powers a surge in Ranbaxy sales. May 9.
Available online at: http://www.fiercepharma.com/story/lipitor-copy-powers-surge-ranbaxy-sales-profits/2012-05-09.

Forbes, 2012. Pfizer feeling Lipitor loss, outlook still solid. February 13.
Available online at: http://www.forbes.com/sites/greatspeculations/2012/02/13/pfizer-feeling-lipitor-loss-outlook-still-solid.

Fox News, 2011. Going green in the operating room. February 21.
Available online at: http://www.foxnews.com/health/2011/02/21/going-green-operating-room.

Fries, B., 1975. Optimal ordering policy for a perishable commodity with fixed lifetime. *Operations Research* 23(1), 46–61.

Fujiwara, O., Soewandi, H., Sedarage, D., 1997. An optimal ordering and issuing policy for a two-stage inventory system for perishable products. *European Journal of Operational Research* 99(2), 412–424.

Gabay, D., Moulin, H., 1980. On the uniqueness and stability of Nash equilibria in noncooperative games. In: *Applied stochastic control of econometrics and management science*, Bensoussan, A., Kleindorfer, P., Tapiero, C., Editors, North-Holland, Amsterdam, The Netherlands, 271–294.

Gal, T., Stewart, T., Hanne, T., 1999. *Multicriteria decision making advances in MCDM models, algorithms, theory and applications*. International Series in Operations Research & Management Science, Kluwer Academic Publishers, Boston, Massachusetts.

Gatica, G., Papageorgiou, L., Shah, N., 2003. Capacity planning under uncertainty for the pharmaceutical industry. *Chemical Engineering Research and Design* 81(6), 665–678.

Georgiadis, P., Vlachos, D., Iakovou, E., 2005. A system dynamics modeling framework for the strategic supply chain management of food chains. *Journal of Food Engineering* 70, 351–364.

Ghandforoush, P., Sen, T., 2010. A DSS to manage platelet production supply chain for regional blood centers. *Decision Support Systems* 50(1), 32–42.

Giusti, L., 2009. A review of waste management practices and their impact on human health. *Waste Management* 29(8), 2227–2239.

Gong, Y., Chen, X., 2010. Healthcare information integration and shared platform based on service-oriented architectures. 2nd International Conference on Signal Processing Systems (ICSPS), Dalian, China.

Goyal, S., Giri, B., 2001. Recent trends in modeling of deteriorating inventory. *European Journal of Operational Research* 134, 1–16.

Grocery Manufacturers of America, 2004. 2004 unsalables benchmark report.
Available online at: http://www.gmabrands.com/industryaffairs/docs/benchgma2004.pdf.

Haijema, R., 2008. Solving large structured Markov decision problems for perishable – inventory management and traffic control, Ph.D. thesis. Tinbergen Institute, The Netherlands.

Haijema, R., van der Wal, J., van Dijk, N., 2007. Blood platelet production: Optimization by dynamic programming and simulation. *Computers and Operations Research* 34, 760–779.

Harland, C., 1996. Supply chain management: Relationships, chains and networks. *British Journal of Management* 7, S63–S80.

Harris, G., 2011. Deal in place for inspecting foreign drugs. *The New York Times*. August 13.
Available online at: http://www.nytimes.com/2011/08/13/science/13drug.html?scp=1&sq=deal%20in%20place%20for%20inspecting%20foreign%20drugs&st=cse.

Hartman, P., Stampacchia, G., 1966. On some nonlinear elliptic differential functional equations. *Acta Mathematica* 115, 271–310.

Harvard Medical School, 2003. Drug expiration dates – Do they mean anything? The Harvard Medical School Family Health Guide.

Hernando, M., Mezcua, M., Fernandez-Alba, A., Barcelo, D., 2006. Environmental risk assessment of pharmaceutical residues in wastewater effluents, surface waters and sediments. *Talanta* 69(2), 334–342.

Higgins, M., Rodriguez, D., 2006. The outsourcing of R&D through acquisitions in the pharmaceutical industry. *Journal of Financial Economics* 80, 351–383.

Hunt, J., 2012. Red Cross to close daily blood donation center. *Charleston Daily Mail*. December 17.
Available online at: http://www.dailymail.com/News/201212160118.

Hwang, H., Hahn, K., 2000. An optimal procurement policy for items with an inventory level-dependent demand rate and fixed lifetime. *European Journal of Operational Research* 127(3), 537–545.

Jacobs, D., Silan, M., Clemson, B., 1996. An analysis of alternative locations and service areas of American Red Cross blood facilities. *Interfaces* 26(3), 40–50.

Jennings, J., 1973. Blood bank inventory control. *Management Science* 19(6), 637–645.

Jesson, J., Pocock, R., Wilson, K., 2005. Reducing medicines waste in the community. *Primary Health Care Research and Development* 6, 117–124.

Jia, J., Hu, Q., 2011. Dynamic ordering and pricing for a perishable goods supply chain. *Computers & Industrial Engineering* 60, 302-309.

Johnson, T., 2011. The debate over generic-drug trade. Council on Foreign Relations. August 3.
Available online at: http://www.cfr.org/drugs/debate-over-generic-drug-trade/p18055#p2.

Jones, D., Mirrazavi, S., Tamiz, M., 2002. Multi-objective meta-heuristics: An overview of the current state-of-the-art. *European Journal of Operational Research* 37, 1–9.

Karaesmen, I., Scheller-Wolf, A., Deniz B., 2011. Managing perishable and aging inventories: Review and future research directions. In: Kempf, K., Kskinocak, P., Uzsoy, P., Editors, *Planning production and inventories in the extended enterprise*. Springer, Berlin, Germany, 393–436.

Karamardian, S., 1969. Nonlinear complementary problem with applications, Part I and II. *Journal of Optimization Theory and Applications* 4, 87-98, 167–181.

Katsaliaki, K., Brailsford, S., 2007. Using simulation to improve the blood supply chain. *Journal of the Operational Research Society* 58, 219–227.

Keeney, R., Raiffa, H., 1976. *Decisions with multiple objectives*. John Wiley & Sons, New York.

Kendall, K., Lee, S., 1980. Formulating blood rotation policies with multiple objectives. *Management Science* 26(11), 1145–1157.

Kinderlehrer, D., Stampacchia, G., 1980. *An introduction to variational inequalities and their applications*. Academic Press, New York.

Kopach, R., Balcioglu, B., Carter, M., 2008. Tutorial on constructing a red blood cell inventory management system with two demand rates. *European Journal of Operational Research* 185(3), 1051–1059.

Lambert, D., Adams, R., Emmelhainz, M., 1997. Supplier selection criteria in the healthcare industry: A comparison of importance and performance. *International Journal of Purchasing and Materials Management* 33, 16–22.

Levin, Y., McGill, J., Nediak, M., 2010. Optimal dynamic pricing of perishable items by a monopolist facing strategic consumers. *Production and Operations Management* 19(1), 40–60.

Lin, Y.-H., 2010. Delivery of critical items in a disaster relief operation: Centralized and distributed supply strategies. Ph.D. thesis in Industrial and Systems Engineering, The University at Buffalo, State University of New York.

Liu, Z., Nagurney, A., 2011a. Supply chain outsourcing under exchange rate risk and competition. *Omega* 39, 539–549.

Liu, Z., Nagurney, A., 2011b. Risk reduction and cost synergy in mergers and acquisitions via supply chain network integration. *Journal of Financial Decision Making* 7(2), 1–18.

Liu, Z., Nagurney, A., 2012a. Multiperiod competitive supply chain networks with inventorying and a transportation network equilibrium reformulation. *Optimization and Engineering* 13(2), 471–503.

Liu, Z., Nagurney, A., 2012b. Supply chain networks with global outsourcing and quick-response production under demand and cost uncertainty. *Annals of Operations Research*, in press.

Lowman, M., Trott, P., Hoecht, A., Sellam, Z., 2012. Innovation risks of outsourcing in pharmaceutical new product development. *Technovation* 32, 99–109.

Maon, F., Lindgreen, A., Vanhamme, J., 2009. Developing supply chains in disaster relief operations through cross-sector socially oriented collaborations: A theoretical model. *Supply Chain Management: An International Journal* 14(2), 149–164.

Marler, R., Arora, J., 2004. Survey of multi-objective optimization methods for engineering. *Structural and Multidisciplinary Optimization* 26, 369–395.

Martinez, M., 2011. Contingency planning for natural disasters. *ISBT Science Series* 6(1), 212–215.

Marucheck, A., Greis, N., Mena, C., Cai, L., 2011. Product safety and security in the global supply chain: Issues, challenges and research opportunities. *Journal of Operations Management* 29(7/8), 707–720.

Masoumi, A., Yu, M., Nagurney, A., 2012. A supply chain generalized network oligopoly model for pharmaceuticals under brand differentiation and perishability. *Transportation Research E* 48(4), 762–780.

Melo, M., Nickel, S., Saldanha da Gama, F., 2009. Facility location and supply chain management: A review. *European Journal of Operational Research* 196, 401–412.

Mendoza, M., 2008. More testing for drugs in water sought. *USA Today*. March 3. Available online at: http://www.usatoday.com/news/nation/2008-03-16-3533657499_x.htm.

Mihalopoulos, D., 2009. Expired or lost drugs costing city $1 million. *Chicago Tribune*. February 3.

Millard, D., 1960. Industrial inventory models as applied to the problem of inventorying whole blood, Industrial Engineering analyses of a hospital. *Blood Laboratory, Engineering Experimental Station Bulletin* 180, Ohio State University, Columbus.

Moalem, S., Herbon, A., Shnaiderman, H., Templeman, J., 2010. Off-line and user-oriented approach for supplier selection in dynamic environment: A case study in the healthcare services. *Journal of Service Science and Management* 3, 390–407.

Muller, J., Popke, C., Urbat, M., Zeier, A., Plattner, H., 2009. A simulation of the pharmaceutical supply chain to provide realistic test data. First International Conference on Advances in System Simulation, Porto, Portugal.

Mustafee, N., Katsaliaki, K., Brailsford, S., 2009. Facilitating the analysis of a UK national blood service supply chain using distributed simulation. *Simulation* 85(2), 113–128.

Nagurney, A., 1999. *Network economics: A variational inequality approach*, second and revised edition, Kluwer Academic Publishers, Dordrecht, The Netherlands.

Nagurney, A., 2006. *Supply chain network economics: Dynamics of prices, flows and profits*. Edward Elgar Publishing Inc., Cheltenham, UK.

Nagurney, A., 2009. A system-optimization perspective for supply chain network integration: The horizontal merger case. *Transportation Research E* 45, 1–15.

Nagurney, A., 2010a. Supply chain network design under profit maximization and oligopolistic competition. *Transportation Research E* 46, 281–294.

Nagurney, A., 2010b. Optimal supply chain network design and redesign at minimal total cost and with demand satisfaction. *International Journal of Production Economics* 128, 200–208.

Nagurney, A., 2010c. Formulation and analysis of horizontal mergers among oligopolistic firms with insights into the merger paradox: A supply chain network perspective. *Computational Management Science* 7, 377–401.

Nagurney, A., Aronson, J., 1989. A general dynamic spatial price network equilibrium model with gains and losses. *Networks* 19(7), 751–769.

Nagurney, A., Cruz, J., Dong, J., Zhang, D., 2005. Supply chain networks, electronic commerce, and supply side and demand side risk. *European Journal of Operational Research* 164, 120–142.

Nagurney, A., Dupuis, P., Zhang, D., 1994. A dynamical systems approach for network oligopolies and variational inequalities. *Annals of Regional Science* 28, 263–283.

Nagurney, A., Masoumi, A., 2012. Supply chain network design of a sustainable blood banking system. In: Boone, T., Jayaraman, V., Ganeshan, R., Editors, *Sustainable supply chains: Models, methods and public policy implications. International Series in Operations Research & Management Science* 174, 49–70, Springer, London, England.

Nagurney, A., Masoumi, A., Yu, M., 2012. Supply chain network operations management of a blood banking system with cost and risk minimization. *Computational Management Science* 9(2), 205–231.

Nagurney, A., Nagurney, L., 2010. Sustainable supply chain network design: A multicriteria perspective. *International Journal of Sustainable Engineering* 3, 189–197.

Nagurney, A., Nagurney, L., 2012. Medical nuclear supply chain design: A tractable network model and computational approach. *International Journal of Production Economics* 140(2), 865–874.

Nagurney, A., Nagurney, L., Li, D., 2012. Securing the sustainability of global medical nuclear supply chains through economic cost recovery, risk management, and optimization. *International Journal of Sustainable Transportation*, in press.

Nagurney, A., Qiang, Q., 2009. *Fragile networks: Identifying vulnerabilities and synergies in an uncertain world.* John Wiley & Sons, Hoboken, New Jersey.

Nagurney, A., Woolley, T., 2010. Environmental and cost synergy in supply chain network integration in mergers and acquisitions. In: Ehrgott, M., Naujoks, B., Stewart, T., Wallenius, J., Editors, *Sustainable Energy and Transportation Systems*, Proceedings of the 19th International Conference on Multiple Criteria Decision Making, Lecture Notes in Economics and Mathematical Systems. Springer, Berlin, Germany, 51–78.

Nagurney, A., Yu, M., 2012. Sustainable fashion supply chain management under oligopolistic competition and brand differentiation. *International Journal of Production Economics, Special Section on Green Manufacturing and Distribution in the Fashion and Apparel Industries* 135, 532–540.

Nagurney, A., Yu, M., Qiang, Q., 2011. Supply chain network design for critical needs with outsourcing. *Papers in Regional Science* 90(1), 123–143.

Nagurney, A., Yu, M., Qiang, Q., 2012. Multiproduct humanitarian healthcare supply chains: A network modeling and computational framework, Proceedings of the 23rd Annual POMS Conference, Chicago, Illinois, April 20-23.

Nagurney, A., Zhang, D., 1996. *Projected dynamical systems and variational inequalities with applications.* Kluwer Academic Publishers, Boston, Massachusetts.

Nahmias, S., 1982. Perishable inventory theory: A review. *Operations Research* 30(4), 680–708.

Nahmias, S., 2011. *Perishable inventory systems.* Springer, New York.

Nahmias, S., Pierskalla, W., 1973. Optimal ordering policies for a product that perishes in two periods subject to stochastic demand. *Naval Research Logistics Quarterly* 20(2), 207–229.

Nash, J., 1950. Equilibrium points in n-person games. Proceedings of the National Academy of Sciences, USA 36, 48–49.

Nash, J., 1951. Noncooperative games. *Annals of Mathematics* 54, 286–298.

Niziolek, L., 2008. A simulation-based study of distribution strategies for pharmaceutical supply chains. Ph.D. thesis in Industrial Engineering, Purdue University, Indiana.

Oliver, R., Webber, M., 1982. Supply chain management: Logistics catches up with strategy. In: Christopher, M., Editor, *Logistics: The strategic issues*. 1992, Chapman and Hall, London, UK, 63–75.

Oloruntoba, R., Gray, R., 2006. Humanitarian aid: An agile supply chain? *Supply Chain Management* 11(2), 115–120.

Omosigho, S., 2002. Determination of outdate and shortage quantities in the inventory problem with fixed lifetime. *International Journal of Computer Mathematics* 79(11), 1169–1177.

Or, I., Pierskalla, W., 1979. A transportation location-allocation model for regional blood banking. *IIE Transactions* 11(2), 86–95.

Osvald, A., Stirn, L., 2008. A vehicle routing algorithm for the distribution of fresh vegetables and similar perishable food. *Journal of Food Engineering* 85, 285–295.

Papageorgiou, L., 2009. Supply chain optimisation for the process industries: Advances and opportunities. *Computers and Chemical Engineering* 33, 1931–1938.

Papageorgiou, L., Rotstein, G., Shah, N., 2001. Strategic supply chain optimization for the pharmaceutical industries. *Industrial & Engineering Chemistry Research* 40, 275–286.

Pareto, V., 1971. *Manual of Political Economy*. Augustus M Kelley Pubs, New York.

Pasupathi, P., Sindhu, S., Ponnusha, B., Ambika, A., 2011. Biomedical waste management for health care industry: A review. *International Journal of Biological and Medical Research* 2(1), 472–486.

Pegels, C., Jelmert, A., 1970. An evaluation of blood-inventory policies: A Markov chain application. *Operations Research* 18(6), 1087–1098.

Perakis, G., Sood, A., 2006. Competitive multi-period pricing for perishable products: A robust optimization approach. *Mathematical Programming* Ser. B 107, 295-335.

Pierskalla, W., 2004. Supply chain management of blood banks. In: Brandeau, M., Sanfort, F., Pierskalla, W., Editors, *Operations Research and Health Care: A handbook of methods and applications*. Kluwer Academic Publishers, Boston, Massachusetts, 103–145.

Prastacos, G., 1984. Blood inventory management: An overview of theory and practice. *Management Science* 30(7), 777–800.

Price, J., 2011. Study finds problem in red blood cells stored for long periods. *The Boston Herald*. July 16.
Available online at: http://bostonherald.com.nyud.net/business/healthcare/view.bg?articleid=1352146&chkEm=1.

Qiang, Q., Nagurney, A., 2012. A bi-criteria indicator to assess supply chain network performance for critical needs under capacity and demand disruptions . *Transportation Research A* 46(5), 801–812.

Qiang, Q., Nagurney, A., Dong, J., 2009. Modeling of supply chain risk under disruptions with performance measurement and robustness analysis. In: Wu, T., Blackhurst, J., Editors, *Managing supply chain risk and vulnerability: Tools and methods for supply chain decision makers*. Springer, Berlin, Germany, 91–111.

Redcrossblood.org, 2010. Donation FAQs.
Available online at: http://www.redcrossblood.org/donating-blood/donation-faqs.

Reimann, M., Schiltknecht, P., 2009. Studying the interdependence of contractual and operational flexibilities in the market of specialty chemicals. *European Journal of Operational Research* 198(3), 760–772.

Riley, W., Schwei, M., McCullough, J., 2007. The United States' potential blood donor pool: Estimating the prevalence of donor-exclusion factors on the pool of potential donors. *Transfusion* 47, 1180–1188.

Rios, J., 2010. Interviews with the medical director for the American Red Cross Northeast Division Blood Services, Dedham, Massachusetts on July 19 and December 6.

Rosen, J., 1965. Existence and uniqueness of equilibrium points for concave n-person games. *Econometrica* 33, 520–533.

Rossetti, C., Handfield, R., Dooley, K., 2011. Forces, trends, and decisions in pharmaceutical supply chain management. *International Journal of Physical Distribution & Logistics Management* 41, 601–622.

Rossi, K., 2011. Several prescription drug patents set to expire. September 13.
Available online at: www.krtv.com/news/several-prescription-drug-patents-set-to-expire.

Rytila, J., Spens, K., 2006. Using simulation to increase efficiency in blood supply chains. *Management Research News* 29(12), 801–819.

Sahin, G., Sural, H., Meral, S., 2007. Locational analysis for regionalization of Turkish Red Crescent blood services. *Computers and Operations Research* 34, 692–704.

Sarker, B., Jamal, A., Wang, S., 2000. Supply chain models for perishable products under inflation and permissible delay in payment. *Computers & Operations Research* 27(1), 59–75.

Schapranow, M., Zeier, A., Plattner, H., 2011. A formal model for enabling RFID in pharmaceutical supply chains. Proceedings of the 44th Hawaii International Conference on System Sciences.

Schneider, M., 2011. Profiteers take advantage of drug shortages. *Family Practice News*. August 16.
Available online at: http://www.familypracticenews.com/news/more-top-news/single-view/profiteers-take-advantage-of-drug-shortages/c5d7e6858b.html.

Schultz, C., Koenig, K., Noji, E., 1996. A medical disaster response to reduce immediate mortality after an earthquake. *The New England Journal of Medicine* 334, 438-444.

Schwab, B., Hayes, E., Fiori, J., Mastrocco, F., Roden, N., Cragin, D., Meyerhoff, R., D'Aco, V., Anderson, P., 2005. Human pharmaceuticals in US surface waters: A human health risk assessment. *Regulatory Toxicology and Pharmacology* 42(3), 296–312.

Shah, N., 2004. Pharmaceutical supply chains: Key issues and strategies for optimisation. *Computers and Chemical Engineering* 28, 929–941.

Sheppard, K., 2011. 2011: The year of the natural disaster. *Mother Jones*. June 22. Available online at: http://motherjones.com/mojo/2011/06/our-disaster-disaster.

Sivakumar, P., Ganesh, K., Parthiban, P., 2008. Multi-phase composite analytical model for integrated allocation-routing problem - application of blood bank logistics. *International Journal of Logistics Economics and Globalisation* 1(3/4), 251–281.

Slonim, A., Bish, E., Xie, R., 2011. Red blood cell transfusion safety: Probabilistic risk assessment and cost/benefits of risk reduction strategies. *Annals of Operations Research*, in press.

Song, X., Cai, X., Chen, J., 2005. Studies on interaction and coordination in supply chain with perishable products: A review. In: Chan, C., Lee, H., Editors, *Successful strategies in supply chain management*. Idea Group Publishing, Hershey, Pennsylvania, 222–248.

Sousa, R., Shah, N., Papageorgiou, L., 2008. Supply chain design and multilevel planning: An industrial case. *Computers and Chemical Engineering* 32, 2643–2663.

Stanger, S., Wilding, R., Yates, N., Cotton, S., 2012. What drives perishable inventory management performance? Lessons learnt from the UK blood supply chain. *Supply Chain Management: An International Journal* 17(2), 107–123.

Subramanian, D., Pekny, J., Reklaitis, G., 2001. A simulation-optimization framework for research and development pipeline management. *American Institute of Chemical Engineers Journal* 47(10), 2226–2242.

Sullivan, M., Cotten, R., Read, E., Wallace, E., 2007. Blood collection and transfusion in the United States in 2001. *Transfusion* 47, 385–394.

Suryawanshi, Y., 2010. Competitive multi-period pricing for perishable products: A robust optimization approach, Ph.D. thesis. Massachusetts Institute of Technology, Cambridge, Massachusetts, the USA.

Szabo, L., 2011. Drug shortages set to reach record levels. *USA Today*. August 15. Available online at: http://yourlife.usatoday.com/health/story/2011/08/Drug-shortages-set-to-reach-record-levels/49984446/1.

The Health Strategies Consultancy LLC, 2005. Follow the pill: Understanding the U.S. commercial pharmaceutical supply chain. Prepared for the Kaiser Family Foundation – March.

The Pakistan Observer, 2011. Voluntary donors increased more than half in 6 years. June 15.
Available online at: http://pakobserver.net/201106/15/detailnews.asp?id=97736.

Tsiakis, P., Papageorgiou, L., 2008. Optimal production allocation and distribution supply chain networks. *International Journal of Production Economics* 111, 468–483.

Tzeng, G.-H., Cheng, H.-J., Huang, T., 2007. Multi-objective optimal planning for designing relief delivery systems. *Transportation Research Part E: Logistics and Transportation Review* 43(6), 673–686.

Van Dijk, N., Haijema, R., Van Der Wal, J., Sibinga, C., 2009. Blood platelet production: A novel approach for practical optimization. *Transfusion* 49(3), 411-420.

WABC, 2008. AG: Pharmacies selling expired products. June 12.
Available online at: http://abclocal.go.com/wabc/story?section=news/local&id=6201355.

Walker, L., 2010. Phone interview with the Director of Business Development for the American Red Cross Blood Services in the Greater Boston Area on July 14.

Wall Street Journal, 2011. US job cuts surge 60% in July on month - Challenger report. Dow Jones Newswires. August 3.
Available online at: http://online.wsj.com/article/BT-CO-20110803-707866.html.

Wang, W., Wang, M., Zhu, S., 2005. Healthcare information system integration: A service oriented approach. Proceedings of 2005 International Conference on Services Systems and Services Management (ICSSSM), Chongqing, China.

Whitaker, B., Green, J., King, M., Leibeg, L., Mathew, S., Schlumpf, K., Schreiber, G., 2007. The 2007 national blood collection and utilization survey report. The United States Department of Health and Human Services.

Wilson, N., 1996. The supply chains of perishable products in northern Europe. *British Food Journal* 98(6), 9–15.

Wolf, A., 2011. Merck set to lay off 13,000. *News Observer*. July 30.
Available online at: http://www.newsobserver.com/2011/07/30/1378418/merck-set-to-lay-off-13000.html.

World Health Organization, 2011. Waste from health-care activities. NEWS Press (English). November 10.
Available online at: http://www.waste-management-world.com/index/from-the-wires/wire-news-display/1538555885.html.

WPRI, 2009. CVS offers $2 for expired products. June 11.
Available online at: http://www.wpri.com/dpp/news/local_news/local_wpri_money_for_expired_products_in_ca_pharmacies_20090611.

Xie, S., Bish, D., Bish, E., Slonim, A., Stramer, S., 2011. Safety and waste considerations in donated blood screening. *European Journal of Operational Research* 217(3), 619–632.

Yang, X., 2006. Choosing transportation alternatives for highly perishable goods: A case study on nuclear medicine, Master's thesis. Massachusetts Institute of Technology, Cambridge, Massachusetts, the USA.

Yegul, M., 2007. Simulation analysis of the blood supply chain and a case study. Master's thesis, Middle East Technical University, Turkey.

Yost, R., 2005. New economics of the pharmaceutical supply chain. *American Journal of Health-System Pharmacy* 62, 525–526.

Yu, M., Nagurney, A., 2013. Competitive food supply chain networks with application to fresh produce. *European Journal of Operational Research* 224(2), 273–282.

Yu, X., Li, C., Shi, Y., Yu, M., 2010. Pharmaceutical supply chain in China: Current issues and implications for health system reform. *Health Policy* 97, 8–15.

Yue, D., Wu, X., Bai, J., 2008. RFID application framework for pharmaceutical supply chain. Proceedings of IEEE International Conference on Service Operations and Logistics, and Informatics, 1125-1130, Beijing, China.

Zacks Equity Research, 2011. Pharmaceutical industry outlook – March.

Zadeh, L., 1963. Optimality and non-scalar-valued performance criteria. *IEEE Transactions on Automatic Control* 8, 59–60.

Zanoni, S., Zavanella, L., 2007. Single-vendor single-buyer with integrated transport-inventory system: Models and heuristics in the case of perishable goods. *Computers and Industrial Engineering* 52, 107–123.

Zhang, L., 2006. Multi-period pricing for perishable products: Uncertainty and competition, Master's thesis. Massachusetts Institute of Technology, Cambridge, Massachusetts, the USA.

Zhou, Y., Yang, S., 2003. An optimal replenishment policy for items with inventory-level-dependent demand and fixed lifetime under the LIFO policy. *The Journal of the Operational Research Society* 54(6), 585–593.